CASE NO. 2014-5054

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

CHERYL KOEHN, Mother and Next Friend of VANNESIA KOEHN,

Appellant,

v.

SECRETARY OF HEALTH AND HUMAN SERVICES,

Appellee.

ON APPEAL FROM THE UNITED STATES COURT OF FEDERAL CLAIMS
NO. 11-355V

BRIEF AND APPENDIX OF APPELLANT

P. Leigh O'Dell
BEASLEY, ALLEN, CROW,
METHVIN, PORTIS, & MILES, P.C.
234 Commerce Street
Montgomery, AL 36103
(334) 269-2343

Attorney for Appellant

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

CHERYL KOEHN v. SECRETARY OF HEALTH AND HUMAN SERVICES
No. 11-355V

CERTIFICATE OF INTEREST

Counsel for the Appellant Cheryl Koehn certifies the following:

1. The full name of every party or amicus represented by me is:

   Cheryl Koehn

2. The name of the real party in interest represented by me is:

   Vanessia Koehn

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

   None

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by in the trial court or agency or are expected to appear in this court are:

   Beasley, Allen, Crow, Methvin, Portis, & Miles, P.C.
   P. Leigh O'Dell

April 21, 2014

/s/ P. Leigh O'Dell
P. LEIGH O'DELL

STATEMENT REGARDING ORAL ARGUMENT

Should the Court desire oral argument, Petitioner stands ready to participate.

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STATEMENT OF RELATED CASES

Pursuant to *Federal Circuit Rule* 47.5, this case has not been before this Court or any other United States Courts of Appeal.

STATEMENT OF JURISDICTION

Cheryl Koehn seeks relief under the Vaccine Act, codified at 42 U.S.C. § 300aa-11. The Court of Federal Claims had jurisdiction over this case pursuant to 42 U.S.C. § 300aa-12(a). The Court of Federal Claims issued a final order on December 9, 2013, denying Petitioner-Appellant's motion for review of the Special Master's decision. This Court has jurisdiction pursuant to 28 U.S.C. § 1295(a)(3). This appeal is timely under FED. R. APP. P. 4(a)(1)(B), which allows an appeal by any party to be filed within sixty (60) days when a United States officer is a party.

STATEMENT OF THE ISSUES

I. Whether the Special Master arbitrarily and capriciously elevated Ms. Koehn's burden of proof by requiring epidemiological proof in support of her medical theory and acceptance by the medical community.

II. Whether the Special Master arbitrarily and capriciously disregarded Petitioner's expert's testimony.

STATEMENT OF THE CASE

Cheryl Koehn, acting as next friend of her daughter, Vanessia Koehn, petitioned for compensation under the National Childhood Vaccine Injury Act of 1986 ("Vaccine Act"), 42 U.S.C. §§ 300aa-1 to -34. The Petition was referred to Special Master Christian J. Moran. A hearing was held on June 21, 2012. A157-A234. Petitioner offered the testimony of Dr. Michael McCabe, Ph.D. Respondent offered the testimony of Dr. Carlos Rosé. The Special Master ruled in favor of Respondent. *Koehn v. Sec'y of Health & Human Servs.*, 2013 U.S. Claims LEXIS 698 (Fed. Cl. Spec. Mstr. May 30, 2013); *see* Petitioner's Appendix, *infra*, at A-100. Ms. Koehn filed a motion for review with the Court of Federal Claims, which was denied. *Koehn v. Sec'y of Health & Human Servs.*, 2013 U.S. Claims LEXIS 1974 (Fed. Cl. Dec. 3, 2013); *see* Petitioner's Appendix, *infra*, at A-2. Ms. Koehn now appeals to this Court.

STATEMENT OF THE FACTS

I. Vanessia Koehn's Injury

The following facts are undisputed. Vanessia was born on February 23, 1995 in Cedar Rapids, Iowa. Ex. 1. She was a born by C-section, full-term with no complications. Ex. 4, at 14. In 2008, Vanessia Koehn was a healthy thirteen year old female. Ex. 4, at 9; Ex. 6. She had received all required vaccinations without adverse reaction. A-171; Ex. 5. at 21. She has no allergies. Ex. 4, at 11. She was a member of swim and track teams. Ex. 6, at 2.

Vanessia received the first administration of Gardasil, on February 18, 2008, followed by a second HPV vaccination on April 18, 2008, and a third HPV shot on August 19, 2008. A-171; Ex. 2, at 3-4. Each of the three shots was administered at the medical office of Dr. Elena R. Regala in Santa Maria, California. Ex. 3, at 6, 8, and 11.

On June 24, 2008, Vanessia presented to Dr. Regala with a rash all over her body that had begun three days prior to the office visit. Ex. 3, at 8; see also A-171. Dr. Regala diagnosed Vanessia with an allergic reaction and prescribed Benadryl and prednisone. *Id*.; Ex. 4, at 7. On June 28, 2008, Vanessia presented to the Emergency Room at Marian Medical Center. Ex. 4, at 9-10; 13-14; see also A171-A172. The rash had resolved three days three days prior to the ER visit, but Vanessia was experiencing severe joint pain in multiple joints in the shoulders,

knees, and ankles, accompanied by fever. Ex. 4, at 13-14. Vanessia's joint pain was so severe in her knees and ankles that she was unable to walk at times. *Id.* Vanessia was admitted to Marian Medical Center for further testing. Ex. 4 at 9-10; 13-14. Vanessia continued to have spikes of high fever and severe joint pain. The rash returned after the fever spikes. *Id.*

On June 28, 2008, Vanessia's C-Reactive protein was greater than four times the upper limit of normal at 2.16 (range 0-0.50 mg/dl); her WBC count was 21.9 (range 4.5-11.0); and her segmented neutrophils were elevated 83.2 (range 35-65). *Id.* at 32. On June 30, 2008, her SED rate was also elevated, measuring at 23 MM (range 0-20 MM). (Id.) On July 1, Vanessia's WBC count was again elevated as well as the segmented neutrophils and SED rate. *Id.* at 33.

On July 1, 2008, Vanessia was examined by Dr. Frank Scott. A171-A172. Dr. Scott noted that Vanessia's C-reactive protein and leukocytes were elevated. Ex. 4, at 11-12. Following his consultation, Dr. Scott diagnosed Vanessia with probable Still's Disease (Systemic Onset Juvenile Arthritis). *Id.* She was started on 20 milligrams of prednisone twice a day and discharged on July 2, 2008. *Id.* at 6.

On July 8, 2008, Vanessia was examined by Dr. Miriam Parsa and Dr. Deborah McCurdy, pediatric rheumatologists from the University of California at Los Angeles Health System. They diagnosed Vanessia's condition as systemic Juvenile Idiopathic Arthritis (sJIA). Ex. 5, at 55. During this time frame, Vanessia

experienced pain, joint swelling, stiffness, fluid on the knees, some fever and nausea. *Id.,* at 51-55. Vanessia's sJIA was initially treated with prednisone and Naprosyn. *Id.* at 55. Dr. McCurdy took Vanessia off of prednisone and prescribed etanercept (brand name, Enbrel®). Her symptoms of sJIA were under control.

On August 19, 2008, Dr. Regala administered the third dose of Gardasil to Vanessia. Ex. 2, at 4. On August 25, 2008, just 6 days after the 3rd Gardasil shot, Vanessia experienced a flare-up of sJIA with symptoms of fever, rash, and joint pain. Ex. 8, at 48-49; A-172. When Dr. McCurdy saw Vanessia again on September 3, 2008, she noted that Vanessia had had symptoms of swollen ankles and knees. Dr. McCurdy continued to treat Vanessia through 2010.

During a January 22, 2011 examination, Mrs. Cheryl Koehn refused the flu vaccine on behalf of Vanessia expressing a concern regarding the use of vaccines. Dr. Alice Hoftman was the examining the physician for that visit. The following was noted, "Discussed č mom importance of this vaccine. Mom hesitant b/c Gardasil. D/w Mom – no data but all vaccines and infections can trigger autoimmune response." Ex.5, at 28.

II. Petitioner's Medical Theory of Causation

A. Petitioner Put Forth Preponderant Evidence that Systemic Juvenile Idiopathic Arthritis Is Caused By Pro-Inflammatory Cytokines

Dr. Michael J. McCabe, Jr., Petitioner's expert immunologist,[1] testified to Petitioner's medical theory of causation. According to Dr. McCabe, the cause of

[1] Dr. Michael McCabe, Petitioner's expert, is an immunologist. A159-A164; Ex. 40. Dr. McCabe earned a Ph.D. in Microbiology and Immunology from Albany Medical College. (*Id.*) He served as a Postdoctoral Research Associate at the prestigious Karolinska Institute in Stockholm, Sweden. Thereafter, from 1992 until 2000, Dr. McCabe was on the faculty at Wayne State University where among other positions, he was an Assistant Professor and Director of the Imaging and Cytometry Facility Core Environmental Health Sciences Center, which was involved in molecular cell biology research requiring intracellular cytokine analysis, etc. From 2003 through 2009, Dr. McCabe was an Associate Professor in the Department of Environmental Medicine at the University of Rochester School of Medicine and Dentistry. *Id.* As an Associate Professor at the University of Rochester, Dr. McCabe taught courses to medical and pharmacy students which included such topics as basic immunology, autoimmune disease, and the immune system. A-161 Dr. McCabe was also Director of Immunomodulators and Immunopathogenesis Research Core. *Id.;* Ex. 38, at 1. In this role, Dr. McCabe led a group of scientists in research which focused on how "drugs, chemicals, vaccines, infections modulate the immune response and how does that contribute to disease." A-162.

Dr. McCabe is a Principal Investigator in a NIH funded-study on immunology and the influence of environmental chemicals, metals and other environmental chemicals, metals and other environmental contaminants on the immune response "with the goal of understanding how these may serve as environmental triggers to autoimmune or immune-mediated diseases." A-160. Dr. McCabe serves on a variety of Research and Regulatory Committees including the NIH's National Institute of Environmental Health Sciences, the U.S. Department of Defense's Congressionally-Directed Medical Research Program, and the WHO International Programme of Chemical Safety, Harmonization Project. A162-A163. Dr. McCabe has authored approximately forty peer-reviewed articles (A-160) in the area of immunology and toxicology, and twelve book chapters (Ex. 40, at 12-13). Dr. McCabe serves on the Editorial Board of the *Journal of Immunotoxicology* and as Associate Editor of *Toxicology and Applied Pharmacology*. He has peer-reviewed papers for the following journals among others, *Journal of Immunology,*

sJIA is thought to be multifactorial – with genetic susceptibility factors and environmental triggers (such as Gardasil) working together to initiate and perpetuate adaptive and innate immune activities resulting in tissue damage. Dr. McCabe testified and scientific literature supports the conclusion that vaccination in genetically susceptible individuals can be an environmental trigger for the development of sJIA. A-173; Ex. 12, at 4 (Berent Prakken et al., *Juvenile idiopathic arthritis*, 377 Lancet 2138 (2011), at 2141 (hereinafter "Prakken")).

Systemic JIA is an autoinflammatory condition. A-173, A177-A178. Systemic JIA involves the dysregulation of various immunological events. Dr. McCabe testified that in patients following an environmental trigger (such as vaccination) where dysregulation occurs, there is a release of DAMPs (Damage-Associated Molecular Pattern Molecules) which results in the generation of proinflammatory cytokines – primarily, TNF alpha, Interkeukin-1 (IL-1), Interkeukin-6 (IL-6), and Interleukin-18 (IL-18). A-173. These proinflammatory cytokines are mediators of the innate immune system and they interact with elements of the adaptive immune system, such as Natural TREGs and Auto-antigen-specific T-cells. *Id.*

Cell Proliferation, Cellular Microbiology, and *Journal of Pharmacy and Pharmacology*.

Since 2009, Dr. McCabe has been an Adjunct Associate Professor at the University of Rochester School of Medicine and Dentistry and an Associate at Robson Forensic, Inc. A-161; Ex. 40.

Dr. McCabe described the adaptive immune and innate immune systems and how they interface using as a point of reference Figure 1 of the Gregerson and Behrens article. A173-A174; A177-A179; Ex. 36, at 2. Dr. McCabe explained that the innate and adaptive immune systems interact continuously and are intended to be in balance. A-174. When the systems are in balance, the systems react to threats such as an infection, rid the body of the danger (effector function), and then turn off. Exs. 70-71; 86-87. When dysregulation occurs or the systems are no longer in balance, the activities of the adaptive and innate immune systems **perpetuate** causing cell damage and other signs of inflammation. A173-A174; A230-A231; A233; Ex. 36 (Gregerson and Behrens article). Dysregulation is an ongoing process. A230-A231; A306.

Dr. McCabe further testified about the role of the innate immune response and proinflammatory cytokines in the etiology of sJIA. A-176. Citing the Mellins article, Dr. McCabe testified regarding the prominent contribution of the innate immune response to sJIA: "Proinflammatory cytokines, including IL-1, but also IL-6, TNF alpha, are critical proinflammatory cytokines in systemic juvenile idiopathic arthritis, and it's really these proinflammatory cytokines and, as indicated here, interleukin-1 that's driving the disease in initiated individuals." *Id.* These proinflammatory cytokines result in patients having fever, elevated C-reactive protein, elevated neutrophils, and joint pain.

A176-A177; Ex. 13, at 4 (Mellons, et al., *Pathogenesis of systemic juvenile idiopathic arthritis: some answers, more questions*, Nature Rev. Rheumatol., 7, 416, 419 (2011)). Although cytokines were not directly measured, Vanessia's presentation of sJIA was characterized by high spiking fever and elevation of systemic acute phase reactants and other markers of inflammation. Ex. 4, at 32-33. This is evidence of an auto-inflammatory disease process driven by dysregulation of the innate immune system and resulting in elevated proinflammatory cytokines. Ex. 27. T-regulatory cells (TREGS) and B cells in the adaptive immune system are involved in recognition events, i.e., turning on and turning off immune responses. A-178. These cells, which normally counteract innate immune mediators and inflammatory processes, appear deficient in sJIA patients. Ex. 15 (Ronaghy article). Dr. McCabe testified that the reason for this deficiency is multigenic with some individuals being susceptible with or without environmental triggers. A-176. But, that the genetic predisposition in sJIA is connected to cytokine biology. A-177. In sum, it was Dr. McCabe's opinion to a reasonable degree of scientific certainty that sJIA is an autoinflammatory disease process that can be initiated by an environmental trigger such as a vaccine and is driven by the proinflammatory cytokines Interleukin-1, Interleukin-6, TNF alpha, and Interleukin-18. A180.

B. The Petitioner Put Forth Preponderant Evidence That Gardasil Elicits the Proinflammatory Cytokines Implicated in the Development of sJIA

The intent of Gardasil, a prophylactic HPV vaccine, is to prevent certain strains of HPV infection and thus, prevent some HPV-associated diseases. Gardasil is a quadrivalent subunit vaccine composed of the L1 viral capsid proteins from four of the most common disease- associated HPV strains (i.e., HPV strains 6, 11, 16 and 18). A170-A171. The L1 capsid protein is the most important structural component of the vaccine, allowing it to self-assemble into virus-like particles (VLPs). A-180.

In addition to the elicitation of high anti-HPV L1 VLP antibody titers, the potent immunogenicity of Gardasil also manifests as a heterogeneous, polyclonal immune response and an anamnestic response. Gardasil is highly immunogenic, eliciting a response of 100 times over natural infection. Ex. 18, at 105; Ex. 16 (Stanley); Ex. 38, at 10. An anamnestic, or strong secondary response, is a desired property of a vaccine that induces immunological memory and long-term protection. In individuals immunized with HPV-L1 VLPs, high levels of both adaptive and innate immune cytokines are produced. Ex. 26. Notably, many of these same vaccine-elicited cytokines are the pro-inflammatory cytokines that have been implicated in the etiology of sJIA.

Dr. McCabe testified that the Gardasil vaccine elicits a cytokine response which includes the production of proinflammatory cytokines such as IL-1, IL-6, and TNF alpha. A182-A183. In support of his opinion, Dr. McCabe cited the Pinto article, which involved the testing of cytokines after vaccination with the HPV-16 L-1 vaccine which is part of Gardasil. A-182; Ex. 26 (Ligia A. Pinto et al., *HPV-16L1 VLP vaccine elicits a broad-spectrum of cytokine responses in whole blood*, 23 Vaccine 3555 (2005)). The Pinto study design is described as follows: "evaluated innate and adaptive immune system cytokine responses induced by HPV-16 L1 VLP in whole blood (WB) cultures from individuals receiving the vaccine (n = 20) or placebo (n = 4) before and after vaccination. 11 cytokines were measured: IL-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IFN, TNF-alpha, and GM-CSF using multiplex bead assays. The study involved whole blood cytokine induction assays and the measurement of multiple cytokines in the same assay. A182-A183. The results included increases in the cytokines TNF alpha, IL-6 and IL-1beta in the groups vaccinated with the HPV L1 vaccine at 10µg and 1µg, with most of those results being statistically significant. A183-A184; Ex. 26, at 4 (Table 1); see also Ex. 30 (Evans); and Ex. 31 (Emeny). The peer-reviewed article published in the prestigious *Vaccine* journal clearly supported Dr. McCabe's scientific opinion that Gardasil elicits

proinflammatory cytokines, the same proinflammatory cytokines implicated in the development of the sJIA.

In addition, Dr. McCabe testified to another study involving the measurement of cytokines following vaccination with the HPV 16 L-1 vaccine. A185-A186; Ex. 28 (Alfonso García-Piñeres et al., *Cytokine and Chemokine Profiles following Vaccination with Human Papillomavirus Type 16 L1 Virus-Like Particles*, 14 Clinical & Vaccine Immunology 984 (2007) (hereinafter "García-Piñeres")). In the García-Piñeres paper, which was peer-reviewed and published in *Clinical and Vaccine Immunology,* cytokines were measured and displayed in a two dimensional cluster analysis (Figure 2) with red indicating an increase in or upregulation of a particularly cytokine, green indicating a decrease and black, no increase. A-186. Following vaccination, the study showed a sustained increase in pro-inflammatory cytokines IL-1alpha, IL-6, TNF-alpha in most recipients of the vaccine. *Id.*

In support of his opinion that Gardasil-like vaccination elicits proinflammatory cytokines, Dr. McCabe also pointed the Court to the following papers that offered consistent results with the Pinto and García-Piñeres García-Piñeres papers: Evans (Ex. 30) and Emeny (Ex.33). A-187. The Evans paper involved vaccination with the HPV-11 VLP 1, which is also included in

Gardasil. According to Dr. McCabe, the study showed that in individuals with high levels of neutralizing HPV antibodies there was an increase in T-cell proliferation and upregulation of cytokines. *Id.* Though the measurement of cytokines was less comprehensive, the study supports Dr. McCabe's conclusions. The Emeny study also documented an increase in lymphoproliferation as well as increased cytokines following vaccination. *Id.*

Dr. McCabe testified not that Gardasil causes sJIA in all young women who receive the Gardasil vaccine, but that in genetically susceptible individuals, like Vanessia, the vaccine elicits pro-inflammatory cytokines that result in the development of sJIA. A197; A205-A206.

III. Petitioner Presented Preponderant Evidence of a Logical Cause and Effect Relationship Between Gardasil and Vanessia's Development of sJIA

Dr. McCabe testified that Gardasil was a substantial contributing cause of Vanessia's injury. A-191. Prior to receiving the first two shots of Gardasil, Vanessia was a healthy thirteen year old female – no joint pain, no fever, etc. Ex. 4, at 9; Ex. 6. Prior to the administration of Gardasil, she had received all required vaccinations without adverse reaction. Ex. 5, at 21. She has no allergies. Ex. 4, at 11. Vanessia received the first administration of Gardasil, on February 18, 2008, followed by a second HPV vaccination on April 18, 2008. Ex. 2, at 3-4.

Following the second Gardasil shot, on June 24, 2008, Vanessia presented to Dr. Regala with a rash all over her body that had begun three days prior to the office visit. Ex. 3, at 8; see also A-171. On June 28, 2008, Vanessia presented to the Emergency Room at Marian Medical Center. Ex. 4, at 9-10; 13-14; A171-A172. The rash had resolved three days three days prior to the ER visit, but while in the ER, Vanessia experienced severe joint pain in multiple joints in the shoulders, knees, and ankles, accompanied by fever. Ex. 4, at 13-14. On June 28, 2008, Vanessia's C-Reactive protein was greater than two times the upper limit of normal at 2.16 (range 0-0.50 mg/dl); her WBC count was 21.9 (range 4.5-11.0); and her segmented neutrophils were elevated 83.2 (range 35-65). *Id.* at 32. On June 30, 2008, her SED rate was also elevated, measuring at 23 MM (range 0-20 MM). *Id.* On July 1, Vanessia's WBC count was again elevated as well as the segmented neutrophils and SED rate. Ex. 4, at 33. On July 1, 2008, Vanessia was examined by Dr. Frank Scott. A171-A172. Dr. Scott noted that Vanessia's C- reactive protein and leukocytes were elevated. (Id. At 11-12.) Although cytokines were not directly measured, Vanessia's presentation – high spiking fever, elevated C-reactive protein, elevated leukocytes, increased in neutrophils, etc. – are all consistent with increases in "proinflammatory cytokines, namely interleukin-1, TNF alpha, interleukin-18, and IL-6." A-187. Additional compelling evidence of the role of proinflammatory cytokines in Vanessia's disease is the effectiveness of the

therapeutic agents. A187-A188. Vanessia has been treated to positive effect with Enbrel which inhibits TNF alpha and Methotrexate which targets inflammatory processes, including proinflammatory cytokines. A-188.

Dr. McCabe testified that there is a logical sequence of cause and effect between Vanessia receiving the first two Gardasil shots and the onset of sJIA. The Gardasil shots were a trigger that caused the dysregulation of Vanessia's innate immune system. This resulted in proinflammatory cytokines being elicited, which is evidenced by her presentation with fever, rash, joint pain, elevated C- reactive protein, elevated leukocytes, increased in neutrophils, etc. The upregulation of proinflammatory cytokines such as TNF alpha, IL-1, and IL-6 resulted in her sJIA.

Vanessia's treating physicians did not express any opinions as to whether Gardasil was a cause of her development of sJIA. A-196. Dr. Hoftman, one of Vanessia's treating rheumatologists, noted in January 2011, however, that "all vaccines and infections can trigger autoimmune response." Ex.5, at 28.

It is important to note that in reaching the conclusion that Dr. McCabe did testify that Gardasil was the only cause of Vanessia's disease. Nor did Dr. McCabe assert that every person or a large percentage of persons who are vaccinated with Gardasil will suffer from sJIA. Rather, it was Dr. McCabe's opinion that sJIA is rare, but despite its rarity, Vanessia experienced such an occurrence: "I'm not arguing that or I'm not proposing that Vanessia Koehn wasn't somehow

predisposed to the disease or had what we would perhaps agree would be a genetic predisposition to developing the disease, but her development of the disease, manifestation of the disease, required a trigger, and . . . that trigger in the context of everything else we know, . . . was Gardasil." A-197. Dr. McCabe testified that in his opinion Gardasil was not the only cause of Vanessia developing sJIA but that it was a substantial contributing cause, an environmental trigger that "worked in concert with other predisposing factors that make up Vanessia Koehn, and she was for all practical purposes a person who was prone, initiated to developing the disease, and receiving Gardasil at that time was the trigger that caused her disease to manifest." A-206.

IV. Petitioner Put Forth Preponderant Evidence That A Proximate Temporal Relationship Exists Between the Gardasil Vaccinations and the Onset of Vanessia's sJIA

The final prong of *Althen* requires Ms. Koehn to show "a proximate temporal relationship between vaccination and injury." 418 F.3d 1274, 1278. Evidence used to prove one prong of *Althen* can be overlapped to prove another prong as well. *See Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1326 (Fed. Cir. 2006).

Dr. McCabe testified that the expected interval between Gardasil vaccination and the onset of sJIA is predicted by the time period that measurable changes in the

immune response are known to be elicited by the vaccine. A-189. Efficacy studies for Gardasil, based on a three-dose immunization schedule with the second and third doses coming two months and six months, respectively, after the first, show that over 99% of the recipients seroconvert for the vaccine's HPV subtypes within seven months. Ex. 22; see also Exs. 28-30. As detailed in Dr. McCabe's testimony and supplemental report, studies document that vaccine-elicited changes in the cytokine profile occur within the time frame of the standard 3-dose vaccination schedule for Gardasil (i.e., 0, 2, 6 months). A-139; s*ee* Exs. 28-30; 34.)

In Vanessia's case, she received the first administration of Gardasil, on February 18, 2008, followed by a second HPV vaccination on April 18, 2008, and a third HPV shot on August 19, 2008. Ex. 2 at 3-4. On June 24, 2008, Vanessia presented to Dr. Regala with a rash all over her body that had begun three days prior to this office visit, well within the seven-month window described above. Accordingly, Dr. McCabe's testimony and relevant scientific literature regarding the seroconversion of Gardasil are evidence of a strong temporal relationship between Gardasil and Vanessia's injury. A-191.

The Special Master found that Dr. McCabe did not explain the amplification process. A146-A147. Dr. McCabe testified at length regarding the amplification process. A230-A232. As Dr. McCabe explained the amplification process

continues because patient's, like Vanessia, are stimulated with vaccination at 2, and 6 months.

The Special Master further found that Dr. McCabe did not testify that two months is a medically appropriate time period. This finding is clearly erroneous. Dr. McCabe testified that two months was an appropriate interval between vaccination and the onset of injury. A188-A189; A191, A231.

THE STANDARD OF REVIEW

The Court of Federal Claims decision is subject to *de novo* review. *Porter v. Sec'y of Health & Human Servs.*, 663 F.3d 1242 (Fed. Cir. 2011); see *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339 (Fed. Cir. 2010); *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543 (Fed. Cir. 1994). Although the Special Master's findings of fact are upheld unless arbitrary or capricious, this Court owes no deference to either the Special Master or Court of Federal Claims on issues of law. *Broekelschen*, 618 F.3d at 1345.

SUMMARY OF THE ARGUMENT

Petitioner put forth sufficient evidence to satisfy each prong of the *Althen* test. As outlined above, through the testimony of Dr. McCabe, peer-reviewed

medical literature in support of his testimony, and relevant medical records, Petitioner presented preponderant evidence in support of a medical theory causally connecting the vaccination and Vanessia's injury, a logical sequence of cause and effect showing that the vaccination was the reason for the injury, and a proximate temporal relationship between the vaccination and the injury.

The Special Master's decision was arbitrary and capricious because it elevated Petitioner's burden of proof *de facto* requiring the submission of epidemiological evidence and acceptance in the relevant medical community. Moreover, the Special Master failed to consider the record as a whole, arbitrarily disregarding scientific evidence proffered by Petitioner in support of her theory and portions of Dr. McCabe's testimony. The decision of the Special Master should be reversed. The Court of Federal Claims erred when it failed to do so.

ARGUMENT

I. The Special Master Arbitrarily and Capriciously Elevated Petitioner's Burden of Proof under *Althen*

Congress established the Vaccine Injury Compensation Program to award individuals "quickly, easily, and with certainty and generosity." *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1351 (Fed. Cir. 1999). In vaccine cases where the injury is off-table,[2] a petitioner may be awarded compensation by proving by preponderant evidence: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005). A petitioner who satisfies this burden may recover compensation "unless the government shows, also by a preponderance of evidence, that the injury was in fact caused by factors unrelated to the vaccine." *Id.* (internal brackets omitted).

"[T]he purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body." *Althen*, 418 F.3d at 1280. It is intended to encourage the use of circumstantial evidence, and "close calls regarding causation are resolved in

[2] Ms. Koehn does not dispute that sJIA is an off-table injury for Gardasil.

favor of injured claimants." *Id.* A petitioner does not need to prove scientific certainty of her theory to recover under the Act. *Bunting v. Sec'y of Health & Human Servs.*, 931 F.2d 867, 873 (Fed. Cir. 1991).

In this case, the Special Master elevated Petitioner's burden of proof under *Althen* by requiring that Petitioner's theory be supported by epidemiological studies and be generally accepted in the relevant medical community. Doing so was arbitrary and capricious, and should result in the reversal of the decision of the Court of Federal Claims.

A. The Special Master Erred in *De Facto* Requiring Epidemiological Evidence in Support of Petitioner's Medical Theory of Causation under Prong One of *Althen*

A Petitioner need not produce medical literature to establish causation under the Vaccine Act. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367 (Fed. Cir. 2009). Nor is a Petitioner required to submit epidemiological studies to support her theory of causation. The law is clear that epidemiological studies are not required to meet the *Althen* standard. *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1325 (Fed. Cir. 2006); see also *Harris v. Sec'y of Health & Human Servs.*,, 102 Fed. 282, 300 (Fed. Cl. 2011). In *Knudsen by Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543 (Fed. Cir. 1994), the Federal Circuit ruled in favor of petitioners when epidemiological evidence directly opposed causation. *Knudsen*, 35 F.3d at 551.

The Special Master stated in his decision that he "may not find against a petitioner solely because the petitioner did not introduce supporting epidemiology." A-141. Despite this statement, the Special Master analyzed at length two epidemiological studies throughout his decision, and in doing so, gave erroneous weight to the lack of epidemiological evidence in support of Petitioner's medical theory. A107-A110; A128-A129; A141-A143; A155.[3]

The lack of epidemiological evidence to support Petitioner's theory of medical causation is not surprising. The incidence rate of sJIA in children under 16 years old is between 0.3 and 0.8 per 100,000 persons. A-112. Thus, sJIA is a rare but debilitating disease. The low incidence rate in the overall population makes the disease almost, if not, impossible to evaluate in an epidemiological study. The reason for this is that the number of patients in a study would have to be extremely large, hundreds of thousands of patients, in order to be sufficiently powered to render reliable, statistically significant results. Petitioner's expert, Dr. McCabe, analyzed this issue at length during the entitlement hearing, explaining why the epidemiological studies involving HPV vaccines are not relevant for purposes of evaluating whether Gardasil can cause sJIA. A189-A190; A200-A201.

[3] Petitioner raised this issue before the Court of Federal Claims. The Court found no error. A19-A20.

The Chao study involved Gardasil. See Ex. 34 (Chun Chao et al., *Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine*, 271 J. Intern. Med. 193, 202 (2012)). The study did not include a specific endpoint for sJIA, though sJIA was included in the overall diagnosis of Juvenile Rheumatoid Arthritis (JRA). The study did not show a statistically significant increase in the rate of JRA (or consequently, sJIA) among those patients vaccinated with Gardasil. Dr. McCabe testified extensively that the reason why the results of the Chao study were not meaningful in relation to whether Gardasil increases the risk of sJIA. First, the study was not sufficiently powered to evaluate patients with the disease. According to Dr. McCabe, even with 189,000 patients the number of patients was insufficient to obtain a statistically relevant and valid result. A-190. Moreover, the study did not include sJIA as a specific endpoint, limiting the relevance of the study even further. *Id.*

The Special Master also placed an inordinate emphasis on the Verstraeten article that was put forth by the Respondent. Ex. E. The Special Master found that that the results in the Verstraeten study supported a finding that that "a vaccine against human papillomavirus can cause sJIA to be unlikely." A-143; A-223. On cross-examination, Dr. Rosé admitted that the Verstraeten article did not involve the Gardasil vaccine or any portions of the Gardasil vaccine, but was an epidemiological study involving GlaxoSmithKline's HPV vaccine, Cervarix which

provides protection against HPV 16 and 18. A216-A217; Ex. E, at 2. Dr. Rosé admitted that Cervarix contains an adjuvant specifically owned by GlaxoSmithKline, the Adjuvant System AS04, a combination of aluminum salt and MPL. (*Id.*) Gardasil contains a different adjuvant. (*Id.*) Moreover, though Dr. Rosé testified that he would have expected to see one or two cases of sJIA, the text of the article suggests that sJIA was not included as an endpoint of the study. A-217; Ex. E, at Tables 2 and 3. For these reasons, the Special Master's reliance on Verstraeten paper was not well founded. A109-A110; A128; A141-A143; A155.

The Special Master's treatment of these epidemiology studies resulted in the application of an erroneously high standard of proof in contravention of this Court's decision in *Capizzano*. See also *Paluck, et al., v. Sec'y of Health and Human Servs.,* No. 07-889v (Fed. Cl. April 18, 2012) (Lettow, J.) (reversing Special Master Moran's decision denying entitlement where Petitioner had put forth a medical theory with indicia of reliability).

B. The Special Master Required Support of Dr. McCabe's Theory by the Medical Community

A petitioner is not required to prove general acceptance of her theory in the scientific or medical community to satisfy the prongs of *Althen*. *Cedillo v. Sec'y of Health & Human Servs.*, 617 F.3d 1328 (Fed. Circ. 2010); *Capizzano*, 440 F.3d at 1325. Nevertheless, the Special Master improperly elevated Ms. Koehn's burden

of proof by placing inappropriate weight on whether Petitioner's medical theory was generally accepted in the medical community. In its analysis, the Special Master concluded that rheumatologists do not "generally accept the theory that Gardasil can cause sJIA." A-140. In support, the Special Master notes that Dr. Rosé is a pediatric rheumatologist, attends conferences, and conducts research on juvenile rheumatoid arthritis (though not sJIA), and that "it seems likely that if rheumatologists were considering whether Gardasil can cause sJIA, then Dr. Rosé would have heard some discussion about this theory. However, Dr. Rosé testified that he did not recall haring about this." *Id.* Anecdotal testimony from Dr. Rosé that he has not heard about a theory is a wholly inadequate ground on which to reject Ms. Koehn's theory. No evidence was presented at the hearing regarding what conferences Dr. Rosé attended during the relevant time period, whether he had discussions about sJIA with colleagues, or whether he had discussions about the Gardasil vaccine. The Special Master's decision to hold this perceived lack of acceptance in the medical community against Ms. Koehn amounted to a requirement of such support and runs afoul of this Court's decision in *Capizzano*. *See* 440 F.3d at 1325 ("[W]e conclude that requiring . . . general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect is contrary to what we said in *Althen III*.").

II. The Special Master Failed to Consider the Whole Record

A. The Special Master Arbitrarily Disregarded Scientific Evidence Proffered by Petitioner

Failure of a special master to consider the full record. *Dickerson v. Sec'y of Health & Human Servs.*, 35 Fed. Cl. 593, 601 (1996). Ms. Koehn offered scientific articles by Ronaghy, Prakken, and Mellins in support of Dr. McCabe's theory that Gardasil causes the upregulation of pro-inflammatory cytokines, and that these cytokines caused Vanessia's sJIA. *See* Petitioner's Brief, *supra* at 4-16. The Special Master's decision gave little to no weight to these articles in his discussion of *Althen* prong one, preferring instead to focus on two studies cited in the Prakken article. A-135. These studies were inapposite because they contained different vaccines that immunize against different diseases; one study involved the MMR vaccine, and the other involved the meningococcal C vaccine. *Id.* Dr. McCabe testified that Gardasil induces a far more potent immune response than either the MMR or meningococcal vaccines. A-202. The Special Master erroneously interpreted Dr. McCabe's testimony as saying that he did not know whether meningococcal vaccine elicits the same cytokines as Gardasil, when in fact Dr. McCabe unequivocally testified that it does not. A-135; A-202. It was arbitrary of the Special Master to consider these studies in evaluating Dr.

McCabe's theory instead of the published, peer-reviewed articles Ms. Koehn offered that discuss HPV vaccines.

B. The Special Master Arbitrarily and Capriciously Disregarded Portions of Dr. McCabe's Testimony

First, the Special Master arbitrarily and capriciously disregarded Dr. McCabe's testimony regarding the Pinto article. Dr. McCabe is an immunologist who has done extensive research on pro-inflammatory cytokines. Dr. McCabe testified that that the Pinto article evidences that HPV vaccine elicits pro-inflammatory cytokines. A183-A184. As Dr. McCabe explained, the media portion of the study was the control group. *Id.* The media group was the group that was not being stimulated with VLP. A183. The relevant portions of the study were those groups that were stimulated by VLP.

Without sufficient explanation, the Special Master rejected Dr. McCabe's interpretation of the Pinto article, instead relying on the interpretation of Dr. Rosé who asserted that the relevant findings related to the media group not to the other two groups in the study that were stimulated by the VLP (either at 1 microgram or 10 micrograms). The media group's assays were not stimulated with the VLP, and did not produce any significant increase in pro-inflammatory cytokines. A137-A139. Dr. Rosé is not an immunologist and has conducted no research of cytokines. As the Pinto article makes clear, HPV-vaccinated blood that is

stimulated with VLP produces a significant increase in pro-inflammatory cytokines. The Special Master's dismissal of Dr. McCabe's interpretation of the Pinto article without sufficient explanation was erroneous.

Secondly, the Special Master rejected Dr. McCabe's testimony in regard to Prong Two of *Althen* because he does not treat patients. A153-A154. Dr. McCabe's research and experience as an immunologist qualifies him to testify about the effect of vaccines on the human body's immune response, the role of cytokines in immunity, and the implications of dysregulation of a person's immune system. A161-A162. Dr. Rosé's role in treating children with sJIA does not require him to determine the cause of sJIA. Dr. Rosé is not an immunologist, is not steeped in the complexities of cellular biology, has not specifically researched the effect of vaccines, and has not researched pro-inflammatory cytokines. While Dr. Rosé's opinion is not without value, the Special Master's disregard of Dr. McCabe's testimony in regard to Prong Two of *Althen* because he does not treat patients was capricious and arbitrary.

CONCLUSION

Ms. Koehn put forth preponderant evidence under this Court's *Althen* test to satisfy each of the three prongs. The Special Master erroneously elevated Ms. Koehn's burden of proof by requiring epidemiological evidence and general acceptance in the medical community. The Special Master erroneously failed to

consider the whole record and improperly disregarded Dr. McCabe's testimony. Ms. Koehn respectfully urges this Court to reverse the decision of the Court of Federal Claims, find that Ms. Koehn is entitled to compensation under the Vaccine Act, remand this case to the Special Master for proceedings as to damages, and provide any further relief that is just and proper.

Respectfully submitted this 21st day of April, 2014.

/s/ P. Leigh O'Dell
P. Leigh O'Dell
Counsel for Appellant

Of Counsel:

BEASLEY, ALLEN, CROW,
METHVIN, PORTIS, & MILES
P.O. Box 4160
Montgomery, AL 36103
Telephone: (334)-269-2343
Fax: (334)-954-7555
E-mail: leigh.odell@beasleyallen.com

CERTIFICATE OF COMPLIANCE

I hereby certify that this brief contains 7.064 words and complies with the type-volume limitation set forth in FED. R. APP. P. 32(a)(7)(B)(i).

/s/ P. Leigh O'Dell
Of Counsel

PROOF OF SERVICE

I hereby certify that I have electronically filed the foregoing document with the Court using the CM/ECF system, which will send notification of such filing to Respondent's Counsel on this 21st day of April, 2014.

/s/ P. Leigh O'Dell
Of Counsel

APPENDIX

I. Table of Contents

In the United States Court of Federal Claims

No. 11-355V
(Originally Filed: December 3, 2013)
(Reissued: December 19, 2013)[*]

* *

C. K., as Mother and Next Friend of V. K.,

Petitioner,

v.

SECRETARY OF HEALTH AND HUMAN SERVICES,

Respondent.

* *

Vaccine case; off-table claim; *Althen*; petitioner's challenge to the Special Master's decision; HPV vaccine; Gardasil; systemic juvenile idiopathic arthritis

OPINION

Currently before the court is petitioner's motion for review of the Special Master's ruling of May 30, 2013 denying compensation for an injury allegedly caused by a vaccine. The matter is fully briefed, and oral argument was held on October 18, 2013. For the reasons explained below, we deny petitioner's motion for review.

On June 6, 2011, petitioner, C. K., filed a petition for compensation under the National Childhood Vaccine Injury Act, 42 U.S.C. §§ 300aa-1 to-34 (2006) ("Vaccine Act"), on behalf of her minor daughter, V. K. ("V"). The petition alleges that V developed systemic juvenile idiopathic arthritis ("SJIA") because she received two doses of the human papillomavirus

[*] This opinion was initially withheld from publication to provide the parties with a period of time to propose redactions. The court adopted the parties' proposed redactions, which were made to protect petitioner's identity. The opinion is now prepared for release.

("HPV") vaccine. Specifically, petitioner's theory of the case was that the HPV vaccine causes an increase in particular cytokines, the same cytokines are implicated in SJIA, and therefore the HPV vaccine can be a significant factor in causing SJIA. After conducting a hearing, reviewing epidemiological studies, and weighing the evidence provided by the experts, the Special Master concluded that petitioner had failed to establish a persuasive theory of causation and denied petitioner's request for compensation. *See Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013) (hereinafter "Decision").

BACKGROUND[1]

I. Facts

V was born in 1995. She was generally healthy throughout childhood. She had no remarkable medical events for the first twelve years of her life other than asthma. Dr. Elena R. Regala, V's routine physician, administered the first dose of the HPV[2] vaccine in February of 2008 during a regular check-up. The brand of HPV vaccine given to V was Gardasil, which is manufactured by Merck.[3] Gardasil provides immunization against four strands of virus: HPV-6, HPV-11, HPV-16, and HPV-18, and is therefore referred to as a quadrivalent HPV vaccine.

The HPV vaccine contains virus-like particles ("VLP") that were created from the L1 protein of the human papillomavirus. In order to generate a robust immune response sufficient to generate long term immunity, the

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[1] The facts are derived from the Special Master's decision.

[2] There are over 130 strands of HPV. Some of these strands cause warts. Two strains of the virus, HPV 16 and HPV 18, are known to cause cancer. For a more thorough description of symptoms caused by an HPV infection, see Decision at *2.

[3] The other brand of HPV vaccine discussed in some of the studies considered by the Special Master is Cervarix, which provides immunity against HPV strands 16 and 18. Cervarix differs from Gardasil in that it provides immunity against only two strains of HPV and contains a lipid and aluminum salt adjuvant known as AS04.

vaccine contains an adjuvant[4] and is delivered intramusculary. This vaccine can cause the host to produce more antibodies than he or she would have produced in response to a natural infection.

The second dose of Gardasil was given to V on April 18, 2008. On or around June 21, 2008, V experienced a rash all over her body. This caused her on June 24, 2008 to visit Dr. Regala, who prescribed Benadryl and prednisone for what Dr. Regala believed to be an allergic reaction. Within three days, V's rash had disappeared. After V stopped taking the prednisone, she developed pain in multiple places including her knees, thighs, and calves. V was admitted to Marian Medical Center on June 28, 2008, for severe joint pain and high fever. While at the hospital, V received medical tests, saw a Rheumatologist, and was prescribed prednisone. On July 2, 2008, she was discharged from the hospital with a presumptive discharge diagnosis of juvenile idiopathic arthritis. At the time she was discharged, V no longer had a fever or joint pain but still had a rash.

The cause of SJIA is unknown. The annual incidence rate of this disease in children less than 16 years of age is between 0.3 and 0.8 out of every 100,000. Children with SJIA exhibit symptoms of arthritis and a recurring fever for at least two weeks as well as a rash, enlargement of the liver or spleen, lymphadenopathy, or serositis. When a child with SJIA has active inflamation, commonly referred to as a flare, he or she may experience muscle pain, pain in more than one joint, a fever, and a rash. SJIA may also cause problems with the heart, liver, or in rare cases, the central nervous system.

Many of the symptoms described above are associated with a dysfunction of the innate immune response and a corresponding increase in the production of pro-inflammatory cytokines. A cytokine is a protein which is released almost immediately by certain cells when they come into contact with a specific antigen. When the cytokine is released it signals other cells to generate an immune response. In short, cytokines are like smoke signals which cells send out to indicate the presence of an invasion and to elicit a defensive response. Respondent's expert testified that the cytokine response

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[4] The particular adjuvant contained in Gardasil is amorphous aluminum hydroxyphosphate sulfate, which stimulates antibody production.

is almost universal.[5] There are, however, specific cytokines which are recognized as being either anti-inflammatory or pro-inflammatory. Pro-inflammatory cytokines can lead to fever, increased vascular permeability, and increased synovial inflammation. "The specific pro-inflammatory cytokines that have been implicated in the development of SJIA include interleukin ("IL") 1, IL-6, IL-7, IL-8, IL-18, macrophage inhibitory factor, and tumor necrosis factor [("TNF")]." Decision at *8. Because of the involvement of these cytokines, which are part of the innate immune system, SJIA is classified as an autoinflammatory disease as opposed to an autoimmune disease.[6]

SJIA is treated by medications which minimize inflamation, including some combination of the following: any nonsteroidal anti-inflammatory pharmaceutical such as ibuprofen or naproxen; intravenous immunoglobulin; cyclosporine-A; thalidomide; prednisone, which reduces inflamation and generally suppresses the immune system; etanercept, which targets and inhibits TNF; methotrexate, which is a folic acid inhibitor; tocilizumab, which inhibits IL-6 production; and anakinra, which is a IL-1 inhibitor.

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[5] Scientists have identified approximately 40 specific cytokines thus far.

[6] The distinction between an autoimmune and an autoinflammatory disease is made based on the part of the immune system that is dysregulated or out of balance. The immune system is comprised of two systems: the adaptive and innate. These two systems interact continuously to maintain balance. Hr'g Tr. 67-70, June 21, 2012. When the adaptive immune system is dysregulated, the autoantibodies and autoreactive T cells do not function as they would in a healthy individual and the resultant state is called an autoimmune disease. Rheumatoid arthritis is typically understood to be an autoimmune disease. When the innate immune system, which involves cytokine production by monocytes and neutrophils, functions abnormally, then the resulting state is known as an autoinflammatory disease. *See* Elizabeth D. Mellins et al., *Pathogenesis of systemic juvenile idiopathic arthritis: some answers, more questions*, 7 Nature Revs. Rheumatology 416 (2011) (hereinafter "Mellins"). Before this distinction was made between autoimmune and autoinflammatory diseases, most forms of arthritis were generally referred to as autoimmune disorders. SJIA was only recently classified as an autoimmune disease. Some scholars continue to broadly characterize arthritis as an autoimmune disease and include SJIA in this characterization.

After being discharged from the hospital, V saw a pediatric rheumatologist, Dr. Deborah McCurdy, on July 8, 2008, who noted that V's family history included juvenile idiopathic arthritis and concluded that SJIA was a likely diagnosis in this case. Dr. McCurdy recorded that V's vaccinations were up to date and that V had received two of three courses of the HPV vaccine. Dr. McCurdy communicated these findings to Dr. Regala. When Dr. Regala saw V again on August 19, 2008, she administered the third dose of HPV vaccine. At the time that V received the third course of Gardasil, she was no longer taking prednisone but had started etanercept. A physical therapist recorded that on August 25, 2008, V experienced a flare with symptoms of fever, rash, and increased joint pain. Dr. McCurdy saw V again on September 3, 2008. Dr. McCurdy noted that V complained of having some symptoms after stopping prednisone and that V had swollen ankles and knees. Dr. McCurdy concluded that V had improved but still showed signs of active disease while being treated with methotrexate and etanercept.

Dr. McCurdy continued to care for V through 2010. On January 12, 2011, V visited another pediatric rheumatologist, Dr. Alice Hoftman. During this visit, Dr. Hoftman recommended that V receive the influenza vaccine. Although V had received the influenza vaccine during the previous three years, C. K. refused this treatment for her daughter. Dr. Hoftman recorded that C. K. was hesitant about giving V the vaccine because of Gardasil. Dr. Hoftman explained that there was "'no data but all vaccines and infections can trigger autoimmune response.'" Decision at *10 (quoting Ex. 5 at 28).

II. Expert Opinions

A. Petitioner's Expert

Petitioner offered the testimony of Dr. Michael J. McCabe, Jr., an expert in the field of immunology. Dr. McCabe is not a medical doctor and does not treat patients. In his report, Dr. McCabe wrote that the cause of arthritis is multi-factorial. Genetic susceptibility and environmental triggers such as infections and vaccinations are possible causative factors. Dr. McCabe's theory is essentially that the HPV vaccine, which Dr. McCabe characterized as a potent immunogen, was the environmental trigger that caused V's immune system to fall out balance resulting in her SJIA. The evidence of this is that the vaccine elicited a strong cytokine response which involved the same cytokines that are associated with SJIA.

In support of his theory, Dr. McCabe provided "'scientific and medical literature that implicates pro[-]inflammatory cytokines and inflammatory responses and innate immunity in the pathogenesis of systemic juvenile arthritis.'" Decision at *12 (quoting Hr'g Tr. 123). One such article was Ligia A. Pinto et al., *HPV-16 L1 VLP vaccine elicits a broad-spectrum of cytokine responses in whole blood*, 23 Vaccine 3555 (2005) (hereinafter "Pinto"), which Dr. McCabe interpreted as showing an increase in the production of particular cytokines in response to the HPV vaccine.[7] The Special Master summarized the Pinto study as follows:

> Twenty-four women participated in the study. Blood specimens were collected before the initial injection, known as month zero. Twenty women, then, received a 50 μg dose of vaccination without adjuvant and four women received a placebo of sterile saline solution. One month later, all women were given a second injection of the same substance (either the vaccination or a placebo). At month two, more blood was drawn. At six months, the women received a third injection. At seven months, more blood was drawn.
>
> The researchers determined the level of cytokines for each of the three blood samples after different types of stimulation. This process was done "in vitro," meaning in glass, like a test tube. The blood from women who received the vaccine and women who received the placebo was evaluated in the context of four substances. In the first, the blood was not stimulated at all. The researchers refer to this as the "media." In the second, the blood was stimulated with 10 μg of the virus-like particle present in the vaccine. In the third, the blood was stimulated with 1.0 μg of the virus-like particle. In the fourth, the blood was stimulated with a control known as PHA. The stimulation was for 24 hours in the absence or presence of L1 VLP or PHA.

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[7] The HPV vaccine used in the Pinto study provides immunity against just one strand of HPV, HPV-16, and did not contain an adjuvant. By contrast, the vaccine that V received, Gardasil, provided immunity against four strands of HPV, including HPV-16, and contained an adjuvant.

> . . . . [T]he researchers obtained different results depending upon whether there was any stimulation. For cells in the media–meaning no stimulation–the cytokine levels stayed relatively similar from month zero to month two to month seven. . . . [S]pontaneous secretion of cytokines in the absence of any stimuli (media control) did not show any significant increases following vaccination. For blood that was stimulated either with 10 μg or 1.0 μg of the virus-like particle, cytokines increased. Stimulation of cells from vaccine recipients with L1 VLP (10 μg/ml) induced significant increases in the median levels of inflammatory [] cytokines. Similar patterns of cytokine production to the ones seen in response to L1 VLP at 10 μg/ml were observed when L1 VLP was tested at 1.0 μg/ml.

Decision at *4 (citations and quotations omitted). The Pinto study included a graph that Dr. McCabe used to show how levels of pro-inflammatory cytokines like IL-1 beta, IL-6, and TNF alpha increased in response to direct stimulation with the L1 VLP.[8] Pinto at 3558; *see* Hr'g Tr. 104. According to Dr. McCabe, the particular cytokines that increased in response to the HPV L1 VLP are the same cytokines, IL-1, IL-6, and TNF, that are dysregulated in SJIA. This commonality of cytokines present in response to the HPA vaccine and involved in SJIA is the foundation and mechanistic support for Dr. McCabe's theory of causation.

Dr. McCabe also presented the Special Master with an epidemiological study, which evaluated a database of the medical history of approximately 189,000 women to determine whether these women developed autoimmune conditions within 180 days of receiving the quadrivalent HPV vaccine. Chun Chao et al., *Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine*, 271 J. Intern. Med. 193 (2012)

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[8] This was not the only study Dr. McCabe relied on to show an increase in pro-inflammatory cytokines in response to stimulation with the HPV vaccine. Dr. Pinto participated in a more recent study which also showed "that various cytokines increased after the administration of a vaccine against human papillomavirus." Decision at *12; *see* Alfonso García-Piñeres et al., *Cytokine and Chemokine Profiles following Vaccination with Human Papillomavirus Type 16 L1 Virus-Like Particles*, 14 Clinical & Vaccine Immunology 984 (2007) (hereinafter "García-Piñeres").

(hereinafter "Chao"). One of the diseases that the researchers targeted was juvenile rheumatoid arthritis[9] ("JRA"). In order to identify JRA within the population, the researchers looked for a diagnostic code which included JRA and searched for medications commonly prescribed to treat JRA. While the researchers did not reach any statistically relevant findings regarding JRA, they concluded, "no safety signal for autoimmune conditions was found following HPV4 vaccination in routine clinical use." *Id.* at 202. Dr. McCabe used this study to show that, despite the large population involved in this study, it was not large enough to detect any increase in the rate of SJIA following HPV vaccination because SJIA is such a rare disease. During the hearing, Dr. McCabe explained that there is an absence of epidemiological studies in support of his theory because the disease is too rare for scientists to be able to generate statistically relevant data. Hr'g Tr. 134-35. Dr. McCabe testified that "there is 'no epidemiology that's meaningful enough to inform us' as to whether the HPV vaccine causes sJIA." Decision at *13 (quoting Hr'g Tr. 141-42).

The additional literature which Dr. McCabe relied on in his report to support the connection between vaccines and SJIA was summarized by the Special Master in the following manner:

> Dr. McCabe identified three articles in which the authors stated that infections or vaccinations could be the initial cause for sJIA. Tr. 136, 142-43, 145-46. One article stated, "in juvenile idiopathic arthritis (JIA) a temporal relationship between disease onset, childhood vaccination, remissions and flares hint[s] at a possible relation of JIA disease activity and vaccinations or infections." Exhibit 15 (Arash Ronaghy et al., Vaccination leads to an aberrant FOXP3 T-cell response in non-remitting juvenile idiopathic arthritis, 70 Ann. Rheum. Dis. 2037 (2011)) at 1 [(hereinafter "Roghany")] . . . . Another article asserted that "[o]ne scenario is that infectious agents that are typically encountered in childhood initiate sJIA; no single environmental trigger has been identified, although this lack of an obvious

[9] The researchers did not search for SJIA in particular. However, Dr. Rose believed that "almost certainly all cases of JRA within the study population would have been detected with the methodology utilized by the investigators." Decision at *5 (citations and quotations omitted).

> candidate could point to multiple common agents being capable of initiating sJIA." [Mellins at 417] A third article stated "[i]n juvenile idiopathic arthritis, infections and vaccinations have been suggested as two candidate triggers." Exhibit 12 (Berent Prakken et al., Juvenile idiopathic arthritis, 377 Lancet 2138 (2011)) at 2141 [(hereinafter "Prakken")]. This article continued, "but neither has been confirmed as a trigger because of a scarcity of proper controlled, prospective studies." Id.

Decision at *8 (underlining in original). These articles speculate that there might be a link between vaccination in general and the development of SJIA, but Dr. McCabe suggested that V was most likely predisposed to develop SJIA and that V's environmental trigger, which substantially caused her to develop the disease, was Gardasil. Hr'g Tr. 162, 197.

Dr. McCabe applied the Bradford-Hill criteria for causation to lend credence to his theory. *See* Sir Austin Bradford Hill, *The Environment and Disease: Association or Causation?*, 7 Proc. of the Royal Society of Medicine 295 (1965) (hereinafter "Bradford-Hill"). Dr. McCabe believes that the temporal sequence, the dose-response relationship, biological plausibility, and experimental evidence, all of which are indicative of causation under the Bradford-Hill assessment, showed that Gardasil could cause SJIA. Dr. McCabe acknowledged that some of the Bradford-Hill criteria, such as strength of association and analogy, were not necessarily supportive of his theory of causation.

Regarding the dose-response correlation, Dr. McCabe pointed to evidence that V experienced a flare after receiving the third dose of HPV vaccine. While acknowledging that V was receiving anti-inflammatory treatments when she received the third dose, which made the causation of this flare less than clear, Dr. McCabe suggested that the worsening of symptoms such as fever, rash, and joint pain during this flare showed that V was generating pro-inflammatory cytokines in response to the third dose of vaccination.

Dr. McCabe also noted that studies showed that almost all of the patients who received the HPV vaccine seroconverted, or developed sufficient antibodies for immunity, within seven months. Based on that data, Dr. McCabe concluded that development of disease within seven months after receiving an HPV vaccine was evidence of a proximate temporal relationship.

B. Respondent's Expert

Dr. Carlos Rose, an expert in the field of pediatric rheumatology, testified on behalf of the Secretary of Health and Human Services. As a pediatric rheumatologist, Dr. Rose routinely treats children with SJI–Dr. Rose, however, is not an immunologist, he has not done any research on the HPV vaccine, and he has not researched the role of pro-inflammatory cytokines in SJIA. After reviewing the literature and Dr. McCabe's report, Dr. Rose concluded that it was mere coincidence that V developed SJIA shortly following her second dose of HPV vaccine. Although Dr. Rose acknowledged that there is some overlap in the cytokines, particularly IL-1 and IL-6,[10] present in those recently vaccinated against HPV and those who have SJIA, Dr. Rose concluded that this overlap was more likely due to the limited number of cytokines that are involved in the stereotypical inflammatory response rather than due to a causal relationship with the vaccine.

In response to the research cited by Dr. McCabe regarding the connection between the HPV vaccine and SJIA, Dr. Rose opined that these articles were simply hypothesis-generating and did not represent a scientific consensus based on evidence and testing. Instead, Dr. Rose explained that, in his experience, pediatric rheumatologists generally discuss the safety of HPV vaccine for their patients and are not asserting links between SJIA and vaccines.

Dr. Rose also provided his interpretation of the relevance of the Pinto study. The media group, i.e. the group not stimulated in vitro, was the most relevant to Dr. Rose because it showed a lack of sustained cytokine response one month after each dose of vaccination. Dr. Rose observed that the cytokine response in this media group remained relatively consistent at months zero, two, and seven. This, according to Dr. Rose, is "'very suggestive that the response that this vaccine elicited in these normal people has not been sustained.'" Decision at *17 (quoting Hr'g Tr. 225). By contrast, patients with SJIA experience a pattern of up-regulated cytokines, which is why they are treated with medications that inhibit these specific cytokines. Dr. Rose

[10] "Dr. Rose stated that his experience as a clinician who has seen some (but not all) patients with sJIA improve after taking drugs that control interleukin 1 and interleukin 6 informs his belief that these cytokines play a role in the disease." Decision at *16.

disagreed that the Pinto or García-Piñeres studies showed how a vaccine, which may trigger a temporary cytokine response, can cause permanent cytokine dysregulation resulting in disease.

In support of his assertion that SJIA is not caused by the HPV vaccine, Dr. Rose cited an epidemiological study of roughly 60,000 individuals that found no "evidence of an overall increase in relative risks for autoimmune disorders in participants receiving vaccines containing AS04." Thomas Verstraeten et al., *Analysis of adverse events of potential autoimmune aetiology in a large integrated safety database of AS04 adjuvant vaccines*, 26 Vaccine 6630, 6633 (2008) (hereinafter "Verstraeten") (comparing the development of autoimmune diseases in recipients of three different vaccines, only one of which was an HPV vaccine known as Cevarix, containing the adjuvant AS04 against a control group of recipients of vaccines that did not contain AS04 and finding that there was no greater risk of autoimmune disease in the population exposed to AS04).[11] Dr. Rose believed that this study would have shown a connection between SJIA and the HPV vaccine if one existed.

C. Additional Studies the Special Master Considered

Part of the Bradford-Hill criteria referenced by Dr. McCabe is causation judged by analogy, i.e. whether similar vaccines cause results that are similar to those alleged by petitioner. Bradford-Hill at 299. To explore this criteria of causation, the Special Master looked at analogous studies which evaluated whether there was a connection between SJIA and the meningococcal C vaccine or the measles, mumps, and rubella ("MMR") vaccine. Decision at *22; *see* Marloes W. Heijstek et al., *Safety of measles, mumps, and rubella vaccination in juvenile idiopathic arthritis*, 66 Ann. Rheum. Dis. 1384 (2007) (hereinafter "Heijstek"); Evelien Zonneveld-Huijssoon et al., *Safety and Efficacy of Meningococcal C Vaccination in Juvenile Idiopathic Arthritis*, 56 Arthritis & Rheumatism 639 (2007) (hereinafter "Zonneveld-Huijssoon"). The subjects of these studies already had juvenile idiopathic arthritis or SJIA and

[11] At the hearing, the weaknesses of this study were discussed, including the fact that the study did not involve Gardasil or the adjuvant contained in Gardasil and that the researchers looked for JRA rather than SJIA. Hr'g Tr. 240-44. Dr. Rose also conceded that a proper epidemiological study of SJIA would have to test at least 100,000 individuals because of the rarity of the disease. Hr'g Tr. 245-46.

the researchers sought to determine whether the subjects' disease symptoms worsened after receiving either the meningococcal C or the MMR vaccine. The conclusion was the same in each study: the researchers did not observe any flares or worsening of disease activity in the subjects with SJIA or juvenile idiopathic arthritis following vaccination.

According to Dr. Rose, these studies show that the meningococcal vaccine and the MMR vaccine are safe for use in patients with SJIA. Because of this record of safety, Dr. Rose added that Pediatric Rheumatologists recommend that their patients receive all vaccines, except those containing live viruses. Hr'g Tr. 222.

III. The Special Master's Analysis

In order to receive compensation for an injury caused by a vaccine other than those injuries listed on the Vaccine Injury Table,[12] a petitioner must,

> show by preponderant evidence that the vaccination brought about her injury by providing: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury.

Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005); *see* 42 U.S.C. § 300aa-13(a)(1)(A). Petitioner "must provide a reputable medical or scientific explanation that pertains specifically to the petitioner's case, although the explanation need only be 'legally probable, not medically or scientifically certain.'"[13] *Moberly v. Sec'y of Health & Human*

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[12] *See* 42 U.S.C. § 300aa-14(a) (injury table); *W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1356 (Fed. Cir. 2013) (explaining that "[i]n a table claim, the petitioner benefits from a statutory presumption of causation upon showing that the injury is listed in the Vaccine Injury Table for the vaccine received and occurred within the time period in the table" but that "[i]f the injury is not listed in the table, the petitioner must prove actual causation by a preponderance of the evidence").

[13] "[A] finding of causation in the medical community may require a (continued...)

Servs., 592 F.3d 1315, 1322 (Fed. Cir. 2010) (quoting *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548-49 (Fed. Cir. 1994)). The theory presented by petitioner need only be more likely than not and "close calls regarding causation are resolved in favor of injured claimants." *Althen*, 418 F.3d at 1280. "Nonetheless, the petitioner must do more than demonstrate a 'plausible' or 'possible' causal link between the vaccination and the injury; he must prove his case by a preponderance of the evidence." *W.C.*, 704 F.3d at 1356.

If petitioner establishes a prima facie case under the *Althen* elements, then the burden shifts to the government to show "'also by a preponderance of evidence, that the injury was in fact caused by factors unrelated to the vaccine.'" *Id.* (quoting *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 547 (Fed. Cir. 1994)).

The Special Master analyzed each prong of *Althen* in turn. Pursuant to prong one of *Althen*, the Special Master considered whether petitioner presented a reliable scientific theory under the framework of *Daubert v. Merrell Dow Pharmaceutical, Inc.*, 509 U.S. 579, 592-95 (1993), whether petitioner's theory originated within the scientific community or arose for the purposes of litigation, and whether the epidemiological evidence supported petitioner's theory.

First, the Special Master assessed the reliability of Dr. McCabe's theory by applying three[14] of the following *Daubert* factors:

> (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and, (4) whether the theory or technique enjoys general acceptance within a relevant scientific

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[13](...continued)
much higher level of certainty than that required by the Vaccine Act to establish a prima facie case." *Broekelschen v. Sec'y of Health & Human Servs.*, 89 Fed. Cl. 336, 343 (2009), *aff'd* 618 F.3d 1339 (Fed. Cir. 2010).

[14] The third *Daubert* factor was not considered by the Special Master because neither party introduced evidence regarding the potential rate of error.

community.

Terran v. Sec'y of Health & Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999) (citing *Daubert*, 509 U.S. at 592-95).

In the absence of studies that directly tested petitioner's theory, the Special Master explored the Bradford-Hill causation criteria of analogy. The Special Master considered two types of analogous studies: those that were conducted on animals and those that involved other vaccines. As for the first type, neither party identified a study conducted with animals even though an animal model for macrophage activation syndrome exists, which is similar to SJIA. Dr. Rose explained that the lack of animal studies on this issue was likely attributable to the fact that researchers were pursuing more productive theories. Then the Special Master considered the Heijstek and Zonneveld-Huijssoon studies, which belonged to the second type. These studies showed no disease aggravation when the test subjects who had JIA or SJIA were vaccinated with the meningococcal C or the MMR vaccination. The Special Master wrote that these "studies suggest that when researchers have explored whether vaccinations affect juvenile idiopathic arthritis, they have not found that the vaccine worsens the disease." Decision at *22. The Special Master acknowledged that these studies contained some factual differences from the present case, but concluded that "[b]ecause they are studies, the Heijstek and Zonneveld-Huijssoon findings are entitled to more weight than speculative passages in other articles." *Id.* The Special Master concluded that the analogous evidence weighed against petitioner's case, or was, at best, neutral.

Next, the Special Master observed that Dr. McCabe's theory was unprecedented and had not been published or peer reviewed, although the Special Master noted that Dr. McCabe relied on peer reviewed and published articles in support of his theory. Specifically, the Special Master discussed Dr. McCabe's reliance on the Pinto experiment to show an increase in cytokines seven months after vaccination. Dr. McCabe had drawn that result from the part of the experiment in which researchers had stimulated blood samples from vaccinated individuals with VLP. Dr. Rose agreed with Dr. McCabe that an increase in the cytokine response would follow from direct stimulation with the VLP. However, Dr. Rose opined that the most relevant part of the Pinto study to the present case was the "media" column, which showed that the level of cytokines present in the blood is relatively stable when it is left alone following vaccination. The Special Master found Dr. Rose's interpretation of the Pinto experiment more persuasive. According to the Special Master, this

evidence did not weigh in favor of finding that petitioner's theory is more likely than not.

While the Special Master acknowledged that petitioner had provided the Prakken article, which shows that some scientists may be hypothesizing about a possible link between vaccination and SJIA, the Special Master noted that one equivocal article did not constitute "evidence that the relevant scientific community generally accepts the theory that Gardasil can cause sJIA." Decision at *24. Given that Dr. Rose is the head of pediatric rheumatology at the Alfred I. DuPont Hospital for Children, the Special Master believed that Dr. Rose would know if pediatric rheumatologists were discussing a possible link between Gardasil and SJIA. However, Dr. Rose testified that pediatric rheumatologists were not discussing whether Gardasil caused SJIA. Rather, pediatric rheumatologists, including Dr. Rose, generally recommend that their patients receive all vaccines except those that contain a live virus. The Special Master found that the relevant scientific community, at this time, does not accept the theory that Gardasil can cause SJIA.

Next, the Special Master analyzed the epidemiological studies provided by respondent. One of these articles, authored by Chao, studied the effects of Gardasil in upwards of 189,000 young women. The Special Master noted that the researchers in this study did not find a cluster of autoimmune disease onset in relation the vaccine. The Special Master then turned to the Verstraeten article, which, although he found to be somewhat weak because of the small sample size and because the researchers tested Cervarix instead of Gardasil, "[t]aken together, the Verstraeten and the Chao articles are an additional (but not decisive) reason for finding that Dr. McCabe's theory that a vaccine against human papillomavirus can cause sJIA to be unlikely." Decision at *26.

Lastly, the Special Master noted that Dr. McCabe developed his theory of causation for the purpose of litigation. The Special Master weighed this fact against petitioner's theory under the *Althen* prong-one analysis, which considers whether petitioner has put forth a medical theory causally connecting the vaccination and the injury. After reviewing the totality of petitioner's theory, the Special Master found it problematic that, even if he accepted "the proposition that pro-inflammatory cytokines contribute to the course of sJIA, this observation does not identify the causes of the disease because something must initiate the increase in cytokines." Decision at *8. Ultimately, the Special Master found that Dr. McCabe's theory of causation contained sufficient gaps to make it unpersuasive and petitioner therefore failed to prove

a medical theory that more likely than not the vaccination was causally connected to the injury.

Although the Special Master was not required to reach conclusions about the remaining *Althen* prongs after holding that petitioner had failed to prove prong one, he noted that the record did not support a finding that development of SJIA within a seven-month interval was sufficient to establish a proximate temporal relationship. Specifically, the Special Master found that the Pinto experiment undermined Dr. McCabe's proposed seven-month interval for the onset of SJIA symptoms because the cytokine response to stimulation with VLP was immediate in the Pinto experiment. While Dr. McCabe attempted to explain the delay between vaccination and symptom onset with a theory of amplification, the Special Master saw the media portion of the Pinto study as contradictory because cytokines in this group remained relatively constant over time. Additionally, the Special Master deduced that the evidence provided about V did not persuasively show that she developed SJIA because of the HPV vaccine. After reviewing Dr. McCabe's theory, Dr. Rose's contradictory opinion, and the evidence presented by each expert, the Special Master concluded that petitioner's theory "contain[ed] sufficient gaps to make it unpersuasive." Decision at *26.

DISCUSSION

This court has jurisdiction to review decisions of the special masters in accordance with 42 U.S.C. § 300aa-12. We review the special master's decision under the standard articulated in 42 U.S.C. § 300aa-12(e) and can only set aside "findings of fact or conclusion of law" that were "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 42 U.S.C. § 300aa-12(e)(2); *see Carson v. Sec'y of Health & Human Servs.*, 727 F.3d 1365, 1368 (Fed. Cir. 2013) (describing how the reviewing court should "give no deference to the . . . Special Master's determinations of law, but uphold the Special Master's findings of fact unless they are arbitrary or capricious"). "The arbitrary and capricious standard of review is difficult for [a petitioner] to satisfy with respect to any issue, but particularly with respect to an issue that turns on the weighing of evidence by the trier of fact." *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1360 (Fed. Cir. 2000). "Weighing the persuasiveness of particular evidence often requires a finder of fact to assess the reliability of testimony, including expert testimony, and we have made clear that the special masters have that responsibility in Vaccine Act cases." *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1325

(Fed. Cir. 2010). Special masters have discretion to weigh the evidence and "reversible error is 'extremely difficult to demonstrate'" unless the special master has failed to consider the relevant evidence of record, drawn implausible inferences or failed to articulate a rational basis for the decision. *Lampe* 219 F.3d at 1360 (quoting *Hines v. Sec'y Health & Human Servs.*, 940 F.2d 1518, 1528 (Fed. Cir. 1999)). The reviewing court does "not reweigh the factual evidence, assess whether the special master correctly evaluated the evidence, or examine the probative value of the evidence or the credibility of the witnesses–these are all matters within the purview of the fact finder." *Porter v. Sec'y of Health & Human Servs.*, 663 F.3d 1242, 1249 (Fed. Cir. 2011).

Petitioner makes four challenges to the Special Master's decision. We address each allegation in turn.

I. Whether the Special Master failed to consider the record as a whole

Petitioner claims that the Special Master failed to consider the whole record in his decision. *See Dickerson v. Sec'y of Health & Human Servs.*, 35 Fed. Cl. 593, 601 (1996) ("[F]ailure to examine the full record and provide sufficient findings constitutes error."). Petitioner believes that, if the Special Master had considered the entire record, he would have seen that petitioner presented a plausible theory supported by the scientific evidence and research.

Respondent replies that the Special Master did not exclude any evidence and that he considered "all 'relevant and reliable evidence governed by principles of fundamental fairness to both parties'" as evidenced by the thoroughness of his decision. Resp't's Resp. to Pet'r's Mot. for Review 10 (quoting RCFC, App. B, Rule 8(b)(1)). Once the Special Master thoroughly considered the record, he was entitled to weigh the evidence and conclude that he was not persuaded by petitioner's theory of the case.

We agree that the Special Master was careful to consider all relevant evidence, particularly those pieces on which petitioner relied to support her case. The Special Master discussed the literature that Dr. McCabe cited to show that medical experts were considering whether there is a connection between SJIA and vaccination, and he found these articles to be equivocal. *See* Decision at *8. The Special Master reviewed the content of the Pinto study at length and concluded that Dr. Rose's interpretation of the significance

of the study was more persuasive. Decision at *23-24. Additionally, the Special Master engaged each part of Dr. McCabe's expert opinion in the analysis of his decision. The Special Master also considered relevant evidence and testimony provided by Dr. Rose. The fact that the Special Master found Dr. Rose's expert opinion more persuasive in light of Dr. Rose's testimony and scientific evidence is simply a function of the Special Master's role as fact finder. So long as the Special Master considered the relevant evidence, and we conclude that he did, we cannot disturb his findings on this ground.

II. Whether petitioner's burden of proof was erroneously elevated

A. Whether the Special Master required petitioner to provide epidemiological proof

Petitioner asserts that the Special Master erred by requiring epidemiological proof of petitioner's theory. *See Cappizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1325 (Fed. Cir. 2006) ("[R]equiring either epidemiological studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect . . . . impermissibly raises a claimant's burden."). Petitioner acknowledges that, throughout the Special Master's decision, he asserted that he was not requiring epidemiological proof. Nevertheless, petitioner alleges that, instead of accepting Dr. McCabe's explanation for why there is an absence of epidemiological and animal studies connecting Gardasil and the development of SJIA, the Special Master turned to and placed "inordinate emphasis" on epidemiological studies provided by respondent that were not squarely on point. Pet'r's Mot. for Review 25. In sum, petitioner believes that the Special Master de facto required epidemiological evidence by pointing to the Chao article, which did not find any statistically relevant increase in the development of JRA following vaccination with Gardasil, and the Verstraeten article, which involved a different HPV vaccine, a different adjuvant, and did not target SJIA within the studied pool of individuals.

Respondent argues that the Special Master did not raise the burden of proof. Rather, throughout his decision, the Special Master maintained that petitioner must prove her case by a preponderance of the evidence. *See, e.g.*, Decision at *18, *20, *28. Respondent states, and we agree, that under the preponderance of the evidence standard, simply positing a theory is not enough. Petitioner must provide a theory that is persuasive. *See W.C.*, 704

F.3d at 1356.

The Special Master has discretion to assess the reliability of expert testimony when weighing the persuasiveness of the evidence. *Moberly*, 592 F.3d at 1325. While the special master may not require epidemiological proof of petitioner's theory, *Cappizzano*, 440 F.3d at 1325, he may evaluate contradictory evidence provided by respondent, *Stone v. Sec'y of Health & Human Servs.*, 676 F.3d 1373, 1379-80, *reh'g en banc denied*, 690 F.3d 1380 (Fed. Cir. 2012), *cert. denied*, 133 S. Ct. 2022 (2013), and he may consider the presence or absence of peer reviewed scientific studies in the context of applying the *Daubert* framework for analyzing whether an expert's theory is persuasive, *Terran*, 195 F.3d at 1316 (upholding the special master's approach of "using Daubert's questions as a tool or framework for conducting the inquiry into the reliability of the evidence"); *see Cedillo v. Sec'y of Health & Human Servs.*, 617 F.3d 1328, 1339 n.3 (Fed. Cir. 2010) (listing the case law in which the Court of Appeals for the Federal Circuit upheld the special master's application of the *Daubert* factors).

In this case, the Special Master considered epidemiological and other medical articles in the context of assessing the persuasiveness of the expert opinions using the first *Daubert* factor, which is whether the theory has been or can be tested. *See* 509 U.S. at 593. Throughout his analysis the Special Master considered the evidence presented by both experts. After considering the lack of animal studies, the articles that posited about a connection between SJIA and vaccination, and the studies that showed no worsening of symptoms in subjects with JIA and SJIA after receiving the MMR or the meningococcal C vaccine, the Special Master found that the latter evidence was more persuasive than the former and, therefore, this *Daubert* factor was either neutral or balanced against petitioner. While the Special Master may not require petitioner to prove his case with epidemiological studies, that does not mean that scientific evidence that tends to contradict petitioner's theory must be ignored. The Special Master was squarely within his role as a fact-finder when he weighed the evidence presented to him. Because we are not tasked with reweighing the evidence, and the Special Master's conclusion about the first *Daubert* factor was neither arbitrary nor capricious, we find no error. *See Hulbert v. Sec'y of Health & Human Servs.*, 49 Fed. Cl. 485, 490 (2001), *aff'd*, 35 F. App'x 899 (Fed. Cir. 2002) (deferring to the Special Master's determination that the petitioner's expert did not present an opinion that was as credible as the opinion given by the respondent's expert when analyzed under the *Daubert* framework).

B. Whether the Special Master impermissibly held against petitioner the fact that Dr. McCabe's theory had not been published or peer reviewed

Petitioner asserts the Special Master heightened her burden to something close to scientific certainty by holding against her the fact that Dr. McCabe's theory had not been published and subject to peer review. Rather, plaintiff claims that she met her burden of preponderant evidence by presenting a theory that was in line with published and peer reviewed scientific literature.

Respondent responds that it was permissible for the Special Master to ask whether Dr. McCabe's theory had been published and subject to peer review because it is the second factor of the *Daubert* framework for assessing the reliability of an expert opinion. *See* 509 U.S. at 593. While we agree that it would be problematic if the Special Master had required petitioner uniquely to present a theory that had been tested and peer reviewed, that is not what happened in this case. The Special Master sought indicia of reliability through the use of the *Daubert* framework, and he noted that, "until [V]'s case, there was not even one case report published in the medical journals showing even a temporal sequence in which a Gardasil vaccination preceded sJIA." Decision at *23 (citation omitted). The Special Master did not end his analysis of the second *Daubert* factor there, however. He proceeded to consider the peer reviewed medical evidence presented by petitioner and, after weighing it, concluded, "the evidence relating to peer review and publication does not assist in finding that Dr. McCabe's theory is probable." Decision at *24. The Special Master's finding was not arbitrary or capricious, and it did not impermissibly raise petitioner's burden because it occurred within a larger framework and was not the Special Master's sole reason for concluding that petitioner's theory was unpersuasive.

C. Whether it was in error and raised petitioner's burden when the Special Master considered if rheumatologists generally accept Dr. McCabe's theory

When the Special Master inquired about whether rheumatologist generally accept the theory that Gardasil can cause SJIA, petitioner claims that he impermissibly raised her burden by requiring a theory that is generally accepted within the scientific community. Petitioner cites *Graves v. Secretary*

of Health and Human Services, 101 Fed. Cl. 310, 323 (2011) (reciting that general acceptance of the theory within the medical community is not required). According to petitioner, the Special Master arbitrarily and capriciously relied on Dr. Rose's statement that he did not recall hearing discussion amongst his colleagues about Gardasil causing SJIA.

Respondent contends, and we agree, that the Special Master's inquiry into whether there is general acceptance of Dr. McCabe's theory within the scientific community is permissible as part of the *Daubert* analysis. *See* 509 U.S. at 594. In his analysis of this factor, the Special Master noted that petitioner provided articles, such as Berent Prakken et al., *Juvenile idiopathic arthritis*, 377 Lancet 2138, 2141 (2011), that showed that the scientific community was hypothesizing that vaccinations or infections might trigger SJIA. Decision at *24. Also, the Special Master noted that Dr. Rose testified that pediatric rheumatologists did not accept the theory that Gardasil can cause SJIA and that the general practice of pediatric rheumatologists is to recommend that their patients receive all vaccinations except those that contain a live virus. As between these indications of what the relevant medical community believes about a connection between Gardasil and SJIA, the Special Master found that the relevant scientific community does not generally accept Dr. McCabe's theory. This inquiry, as part of the *Daubert* framework, did not impermissibly raise petitioner's burden of proof

III. Whether the Special Master misinterpreted the Pinto article

Petitioner asserts that the Special Master's findings regarding the Pinto study were contrary to the evidence. First, petitioner alleges that the Special Master was confused in thinking that the Pinto study involved a live strand of HPV. Petitioner points out that there is no evidence of a live human papillomavirus being involved in either V's case or in the Pinto study. The Special Master's statement regarding the live human papillomavirus appeared in the context of the following paragraph in the Special Master's decision:

> Despite contrary testimony from Dr. McCabe . . . , Dr. Rose's focus on the media column is logical. The blood in the media encountered the L1 virus-like particle only in the context of the three doses of vaccination. This pattern resembles what happened to [V] in the sense that no medical record suggests that she was exposed to a living strand of the human papillomavirus. If [V] encountered the human papillomavirus

> after the vaccination, the Pinto article predicts that she would produce a robust immune response like the ones reported for 10 µg and 1.0 µg of the virus-like particle.

Decision at *23. This paragraph, when considered with the Special Master's earlier description of the Pinto study, Decision at *4, shows that the Special Master understood that only VLP was used in the Pinto study. The Special Master's comparison of the reaction of the blood samples when stimulated with VLP to show how the body would react to a natural HPV infection was made to illustrate Dr. Rose's opinion that a robust cytokine response would be expected in response to stimulation. However, the distinction in this case is that V never experienced a stimulant such as a live human papillomavirus or a concentrated dose of VLP as was administered in the Pinto study. This is the reason why Dr. Rose thought that the media group in the Pinto study was more relevant than the stimulated groups. The Special Master's agreement with that analysis was neither erroneous or illogical.

Second, petitioner argues that the Special Master's reliance on Dr. Rose's interpretation of the Pinto study was arbitrary and capricious because Dr. Rose is not an immunologist and has not conducted research involving vaccines or pro-inflammatory cytokines. Dr. Rose was accepted as an expert in pediatric rheumatology and, as such, was qualified to opine about medical studies. The Special Master did not exclude Dr. McCabe's interpretation of the Pinto study, but instead found Dr. Rose's interpretation to be more reliable. *Moberly*, 592 F.3d at 1325-26 ("Assessments as to the reliability of expert testimony often turn on credibility determinations, particularly in cases . . . where there is little supporting evidence for the expert's opinion."). Respondent asserts, and we agree, that, in light of all of the evidence, the Special Master's reliance on Dr. Rose's interpretation of the significance of the Pinto study was within his discretion as the fact-finder.

IV. Whether the Special Master arbitrarily and capriciously weighed the evidence against petitioner

A. Petitioner provided scientific support for her theory, which the Special Master arbitrarily dismissed

Petitioner claims that the Special Master erroneously dismissed scientific support for petitioner's theory. Specifically, in the Special Master's *Althen* prong-one analysis, he "neither cites not considers the Mellins,

Roghany, Prakken, or Emeny articles."[15] Pet'r's Mot. for Review 20. Petitioner argues that, instead of affording proper weight to the aforementioned studies provided by petitioner which were relevant, from respected journals, and peer-reviewed, the Special Master arbitrarily favored analogous, but off-topic, studies authored by Heijstek and Zonneveld-Huijssoon. Petitioner distinguishes the Heijstek and Zonneveld-Huijssoon studies because they involved the meningococcal C and the MMR vaccines, which lack the potency of Gardasil, and involved patients who had already developed SJIA and may have been taking pharmaceuticals to control the disease. Additionally, Dr. McCabe testified that he would expect the meningococcal C vaccine, which is a vaccine against a bacterial infection, to elicit a different cytokine response than the HPV vaccine, which immunizes against a virus. Hr'g Tr. 183-84. These differences between the Heijstek and Zonneveld-Huijssoon studies and the facts of this case, according to petitioner, make the Special Master's reliance on them arbitrary and capricious.

By contrast, respondent argues that the Special Master considered the Prakken, Mellins, Roghany, and Emeny articles but found that they did not support petitioner's theory. While the Special Master did not evaluate each of these articles specifically in the context of prong one, he did reference them throughout his decision and found that the statements that petitioner relied on from these articles were ambiguous. In his decision, the Special Master described the scientific support that petitioner gleaned from the Prakken, Mellins, and Roghany articles and found it to be unpersuasive due to the equivocation in the findings. Decision at *8-9, *13, *16, *22, *24. While the Special Master only briefly mentioned the Emeny article in his decision, he did write that, "[a]t the hearing, relatively little attention was paid to the García-Piñeres article, Emeny article, or the Evans article because Dr. McCabe and Dr. Rose primarily discussed an article by Pinto." Decision at *3. As fact-finder, it is within the province of the Special Master to weigh the evidence and determine whether it is reliable. He plainly was aware of all the articles and was not obligated to unpack them in detail. His treatment of the Prakken, Mellins, Roghany, and Emeny articles was not arbitrary or capricious.

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[15] The "Emeny" article referred to in the quotation above is Rebecca T. Emeny et al., *Cellular Immune Responses to Human Papillomavirus (HPV)–16 L1 in Health Volunteers Immunized with Recombinant HPV-16 L1 Virus-Like Particles*, 188 J. Infectious Diseases 327, 336 (2003) (hereinafter "Emeny").

B. Whether the Special Master arbitrarily and capriciously disregarded Dr. McCabe's testimony

According to petitioner, the Special Master erred by disregarding Dr. McCabe's testimony on prong two because he does not treat patients. Petitioner asserts that Dr. McCabe is qualified to testify about causation even though he would not be qualified to testify about treatment. Petitioner also opines that, while Dr. McCabe was uniquely qualified to testify about the causal connection between Gardasil and SJIA based on his research as an immunologist, Dr. Rose has never focused on causation but instead specializes in treating children with SJIA.

Respondent replies that the Special Master fully considered Dr. McCabe's testimony, including Dr. McCabe's testimony concerning whether V's flare following the third Gardasil dose was indicative of specific causation. Respondent points out that it is the Special Master's prerogative under the law to examine the qualifications and expertise of the witnesses when weighing their opinions, citing *Locane v. Secretary of Health and Human Services*, 685 F.3d 1375, 1380 (Fed. Cir. 2012). Here, the Special Master found more reliable Dr. Rose's opinion that V's vaccination with Gardasil and development of SJIA were unrelated events. This finding is sound under the law and was not arbitrary or capricious given the divergent expert opinions.

Finally, petitioner contends that the Special Master erred by disregarding Dr. McCabe's testimony about the temporal relationship between vaccination and disease. Dr. McCabe explained that a cytokine response may take months to cycle through a period of amplification to eventually manifest as SJIA. Dr. McCabe testified that development of SJIA within seven months of vaccination therefore would be a medically appropriate period for causation because that is the time period when the immune system works to create antibodies against HPV in response to the HPV vaccine. *See* Decision at *27. Timing was thus indicative of causation in V's case, according to Dr. McCabe, because she developed SJIA within four months of her first dose and two months of the second dose.

The Special Master was not persuaded by Dr. McCabe's explanation of the amplification process. "[S]pecifically, Dr. McCabe did not explain why the immune system's production of cytokines would be amplified for weeks and months without a stimulant being present." Decision at *28. The Special

Master found that Dr. McCabe failed to explain how a seven month period is appropriate for causation based on a theory involving the cytokine response when both experts agree the response is almost immediate to an antigen or trigger. The Special Master wrote that "[t]he body's rapid cytokine response appears inconsistent with Dr. McCabe's assertion that the onset of disease could take many months." Decision at *28.

Respondent argues that the Special Master was entitled to find persuasive Dr. Rose's opinion regarding timing, which was that the medically appropriate period for causation should be short if the cause is cytokine related. Dr. Rose's opinion was not the only scientific evidence that suggested a shorter window for causation than Dr. McCabe proposed. The Special Master also drew from data in the Pinto study showing increased cytokines in response to stimulation and compared it to data that demonstrated a low and consistent level of cytokines in the absence of stimulation. The Special Master found that "[t]he Pinto experiment [] undermines the cohesiveness of Dr. McCabe's theory, particularly in regard to timing both for onset of symptoms and duration of symptoms." Decision at *23.

After considering the evidence and testimony from both experts, the Special Master asserted that a finding on *Althen* prong-three was not necessary because petitioner had failed to establish prong-one. Nevertheless, the Special Master noted the following: "In the absence of evidence, it is difficult to find that [petitioner] has met her burden of proof. Even two months is probably too long an interval for a cytokine-driven reaction." Decision at *28. We will not disturb this finding because it was not arbitrary or capricious in light of the evidence.

CONCLUSION

It is not our role to "reweigh the factual evidence, assess whether the special master correctly evaluated the evidence, or examine the probative value of the evidence or the credibility of the witnesses." *Porter*, 663 F.3d at 1249. Because the Special Master's decision was not arbitrary, capricious, or otherwise not in accordance with the law, we affirm his decision. For the reasons set forth above, we deny petitioner's motion for review. The clerk is directed to enter judgment accordingly. No costs.

s/Eric G. Bruggink
ERIC G. BRUGGINK
Judge

16728043

UNITED STATES COURT OF FEDERAL CLAIMS

CHERYL KOEHN,)
as Mother and Next Friend of,)
VANESSIA KOEHN,)
Petitioners,) Case No.
vs.) 11-355V
SECRETARY OF HEALTH AND)
HUMAN SERVICES,)
Respondent.)

**** UNDER SEAL ****

Courtroom 9
Howard T. Markey National Courts Building
717 Madison Place, N.W.
Washington, D.C.
Friday, October 18, 2013
10:00 a.m.
Motion for Review

BEFORE: THE HONORABLE ERIC G. BRUGGINK

Sara J. Vance, CERT, Digital Transcriber

16728043

APPEARANCES:

ON BEHALF OF THE PETITIONER:

PATRICIA LEIGH O'DELL, ESQ.
Beasley, Allen, Crow, Methvin, Portis & Miles, P.C.
218 Commerce Street
Montgomery, Alabama 36104
(334)269-2343
leigh.odell@beasleyallen.com

ON BEHALF OF THE DEFENDANT:

DARRYL R. WISHARD, ESQ.
U.S. Department of Justice - Vaccine
Vaccine/Torts Branch, Civil Division
P.O. Box 146
Benjamin Franklin Station
Washington, D.C. 20044-1046
(202)616-4357
darryl.wishard@usdoj.gov

16728043

P R O C E E D I N G S

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(Proceedings called to order, 10:01 a.m.)

THE COURT: Nice to see you, Ms. O'Dell. Y'all want to make your appearances?

MS. O'DELL: Leigh O'Dell for the Petitioner, Your Honor.

THE COURT: Okay.

MR. WISHARD: And Darryl Wishard for the Respondent, Your Honor.

THE COURT: All right, thank you.

Do you want to stay there, or do you want to come up?

MS. O'DELL: I'll come up.

THE COURT: All right.

MS. O'DELL: If that's okay with you, sir.

THE COURT: Okay. Thank you for coming all the way from Montgomery.

MS. O'DELL: Always good to be in Washington.

THE COURT: I hope you can find something else to do while you're up here.

MS. O'DELL: I'm afraid --

THE COURT: Well, we're open for business now.

MS. O'DELL: I'm afraid it's going to be a quick trip.

THE COURT: Your Government hard at work.

Okay, what's wrong with what Mr. Moran did? Special Master Moran?

MS. O'DELL: Well, Your Honor, may it please the Court, thanks for the opportunity to do more than just share by brief but to share orally about what I do believe Judge or Special Master Moran did wrong in this case. And there are, I believe, five or six specific areas where he either was arbitrary in the fact -- findings of fact or he applied the wrong standard.

So, if I could step back and walk you through what the Petitioner's theory is, the support for it, and where we believe that Special Master Moran got off track.

THE COURT: Okay.

MS. O'DELL: For the Althen Prong One and the Petitioner's theory is essentially this, and as I appreciate the law, the Petitioner has a burden of putting forth preponderant evidence, making it more likely than not, that a legally probable theory had been put forth. That's it.

THE COURT: Legally?

MS. O'DELL: Probable.

THE COURT: Probable would --

MS. O'DELL: Or logical.

THE COURT: -- incorporate -- well, all right, does probability incorporate the burden of proof, then, that it's

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got to be more likely than not with this theory?

MS. O'DELL: I think our overall burden is probable cause, more likely than not.

THE COURT: Mm-hmm.

MS. O'DELL: For the Althen One standard, the Petitioner must put forward a biologically plausible theory. What I --

THE COURT: Okay.

MS. O'DELL: -- what I view as general causation in other contexts or --

THE COURT: Mm-hmm. Well, the notion of plausibility doesn't -- the Government gets its back up on that one, right?

MS. O'DELL: They do.

THE COURT: Let's assume that something other than, well, gee, whiz, we're not going to laugh that out of court is the standard, that it's -- that there's some -- that there's something behind the more likely than not, the feather, in other words, there's got to be something that makes it more than 50 percent.

Assume the Government is right on it that merely plausible is not sufficient, it's got to be something other than mere plausibility.

MS. O'DELL: I understand. And -- but the evidence

-- the evidence that the Petitioners put forth in this case

is more than, you know, some kind of grandiose --

THE COURT: It does more than meet the laugh test.

MS. O'DELL: It does -- it does pass the laugh test without question.

THE COURT: Right.

MS. O'DELL: Because -- but what we don't have to prove is that there is medical literature -- we don't have to put that forth -- medical literature that says Gardasil causes sJIA in X number of cases. That's not our burden.

THE COURT: Right.

MS. O'DELL: And I believe that's what Special Master Moran did, because if you look at our two-part -- and it's a two-part general causation theory -- but both aspects are supported by peer-reviewed literature. If you look at systemic juvenile ideopathic arthritis first, it is a disease that involves the innate and adaptive immune systems. It is characterized by pro-inflammatory cytokines, primarily interleukin-1, interleukin-6, interleukin-18, and TN-alpha -- TNF-alpha, I should say.

THE COURT: Okay, I think that's at least the way the Special Master said it. That's sort of the second part of your logic train that sJIA is, quote, characterized by both -- do we need to worry about the adaptive ones or just

is the innate one sufficient?

MS. O'DELL: I think both are involved.

THE COURT: Okay.

MS. O'DELL: I think the primary, you would argue, would be interleukin-1 and interleukin-6, which I understand those to be innate, but both are involved. The -- that scientific understanding is well supported in the literature.

THE COURT: Okay. But the way -- this is kind of the key to this. You're trying to set up a logical syllogism, and I'm trying to see where it is as the Special Master said it. Do you know what page that was on, Megan?

Okay. It's a one-two thing. The first one is that in effect that there's a cytokine response when you do the vaccine.

MS. O'DELL: Yes, sir. Well, I can -- I think I can do it this way, Your Honor.

THE COURT: All right.

MS. O'DELL: And just -- and I can go back, and I'll take Gardasil first. How about that?

Gardasil is administered in a schedule essentially zero months, one month, six months, three shots.

THE COURT: Right.

MS. O'DELL: And what the Pinto article, as well as the Garcia-Pineres article, but Pinto certainly shows it the

most clearly, supports a conclusion that the Gardasil vaccine when administered causes a statistically significant increase in pro-inflammatory cytokines.

THE COURT: Right.

MS. O'DELL: Interleukin-1, TNF-alpha.

THE COURT: And do you understand the Government disagreed with that?

MS. O'DELL: I do understand that.

THE COURT: Really, that they actually disagree that there's a elevated response, cytokine response?

MS. O'DELL: No, sir, I'm sorry. I misunderstood what you were saying. I mean, Dr. Rose admitted --

THE COURT: Right.

MS. O'DELL: -- that there is a increase or pro-inflammatory cytokine response. Where Dr. Rose and Special Master Moran depart from Pinto, and I think in Special Master Moran's reanalysis of Pinto is one of the primary errors or occasions in the decision where he was arbitrary and capricious --

THE COURT: Okay.

MS. O'DELL: -- in keeping with Graves, the Graves decision, where in the Graves decision the Special Master reinterpreted an article and the conclusions therein. And the Court in that circumstance found that that was arbitrary

and capricious. And in this case, in talking about Gardasil and what Gardasil does upon -- in vaccination particularly after the second shot, the Pinto article concludes that there is a substantial and statistically significant increase in

the relevant pro-inflammatory cytokines for this case.

THE COURT: Mm-hmm.

MS. O'DELL: That finding in the article, which is published in Vaccine, the premier journal for vaccines, is one of the articles actually that was used to have the vaccine approved by the FDA. So, it is a premier piece of the scientific support for the overall vaccine. And it says, upon vaccination, this is what happens.

THE COURT: Yeah.

MS. O'DELL: But when Special Master Moran reviewed the Pinto article -- let me just get to that place in the opinion, sir, and there's quite a discussion about it. It starts on page 38 and goes on to page 40. He begins this discussion by saying, you know, Dr. McCabe's theory is unprecedented, and he goes on to talk about the Pinto article. And he says, "Dr. Rose opined that a different part of the experiment was more meaningful." And that was the media. Do you see that, sir?

THE COURT: Where are we on 38?

MS. O'DELL: Thirty-nine.

THE COURT: Oh, 39.

MS. O'DELL: Just -- it goes over.

THE COURT: Okay, yes, I see that.

MS. O'DELL: Yes, sir. It says, "Dr. Rose testified that the more relevant portion of that study was

the media." Then --

THE COURT: By the way, what -- I was having a hard time understanding what was meant in that chart or in that study by the word "media."

MS. O'DELL: It's the control. And if you look at the study, sir --

THE COURT: All right. And the control of this group was not an unvaccinated group; it was a group that was merely vaccinated, period.

MS. O'DELL: There were some of those in the group that were not vaccinated.

THE COURT: Oh, okay.

MS. O'DELL: And there were -- and I turn to -- just the study section here, there were two groups, and they were randomly assigned. Some received the vaccine, as I appreciate it, and some did not. The group --

THE COURT: Okay. But control in the sense that their blood was not manipulated ex vivo later.

MS. O'DELL: That's right.

THE COURT: Okay.

MS. O'DELL: Because what they're trying to do is to replicate in some measure what's happening in the immune system inside the body with these blood assays. And in the normal course, like Vanessia, she got one shot, and two months later she got another shot.

THE COURT: Mm-hmm.

MS. O'DELL: And in Pinto, they are looking at -- they have placebo, and then they have the media. Dr. Rose testified on cross examination that there was no antigen in the media. In other words, no vaccine. It was in the one-microgram and the 10-microgram columns that you see on the chart on page 4 of Exhibit 26 that shows the relevant findings.

THE COURT: Mm-hmm.

MS. O'DELL: And then because it shows -- that's what happened in Vanessia's case. She was vaccinated. She did receive that stimulus, if you want to call that that, or that antigen. And she -- this study, we believe, plus Garcia-Pineres, but primarily this one, shows that there is more than some way-out-there theory, there is scientific data that shows in patients like Vanessia who received Gardasil, there is statistically significant increase in the pro-inflammatory cytokines. So, you don't look at the media.

That's not the relevant portion. And Mr. McCabe testified at length trying to explain to Special Master Moran that the media is the control.

So, in other words, to use an analogy, Your Honor, in the Vioxx saga, there was the bigger study. And they had a study that showed -- they had a group of patients who took Vioxx. They had a group of patients who took naproxen. That

was the control. And they were testing for the rate of heart attack or myocardial infarction for a patient. And if you take the analysis that Special Master Moran has done in this case, he's basically saying, well, if you're trying to decide if Gardasil -- I mean, excuse me, Vioxx, increases the risk of heart attack, you don't look at the Vioxx group; you look at the naproxen group. I mean, that's how he has misread this article and --

THE COURT: Well, let me make sure that I understand it, then.

MS. O'DELL: Yes, sir.

THE COURT: The media, as you're calling the control group, you're saying that it's -- that this includes people who have not been vaccinated?

MS. O'DELL: It would -- it's -- the important part of it, Your Honor, is they would -- there could be some in there who have been vaccinated, because this is all, but the

-- the media has no antigen or stimulus. It only has the necessary fluids, which I understand are salt and et cetera to keep the assay viable for analysis. So, in other words, these patients would have been vaccinated initially.

THE COURT: Oh, they are -- they all were vaccinated.

MS. O'DELL: Not all of them were, Your Honor.

THE COURT: Oh, oh.

MS. O'DELL: There is a placebo group.

THE COURT: Do we know what --

MS. O'DELL: What the number --

THE COURT: -- percentage that includes?

MS. O'DELL: Let me look, Your Honor.

There were 24 patients in this study, and if you'll look on page 2 of the Pinto article --

THE COURT: Yeah.

MS. O'DELL: -- there were 20 who were vaccinated and four who were not.

THE COURT: Okay. All right. So, let me back up for a minute before you go into more detail on this. The overall results of this analysis are that if you look at the results from -- manipulation sounds like a pejorative term, and I don't mean it to, but the group -- the samples that are manipulated in a Petri dish at either 10 milligrams or one

milligram, there's a dramatic spike in a very short period of time, as I recall, in the -- is titers the right word for IL2 and IL-1 and some others?

And, so, what -- and that's what the Plaintiff wants to use this for, is that when this suggests that if you expose a second and third time or is it a first, second, and third time in the dish? It would be the second and third time in the dish, right?

MS. O'DELL: Yes, sir, that's right.

THE COURT: Okay. Then you get this spike.

MS. O'DELL: That's right. And, Your Honor, but if I could go back, you mentioned titers. This does not measure titers.

THE COURT: Okay. That's -- I wondered --

MS. O'DELL: It's only measuring pro-inflammatory cytokines in that specific way.

THE COURT: Oh, I thought titer was sort of a generic term for any kind of response. No?

MS. O'DELL: I don't understand it to be that way.

THE COURT: Okay. Well, you would know, I'm sure. Okay.

MS. O'DELL: I think when you look at some of the other articles we put into the record, JURA comes to mind, they talk about seroconversion and antibody titers --

THE COURT: Mm-hmm.

MS. O'DELL: -- that's the context that I think that that term is the most appropriate.

THE COURT: Okay. All right. But I don't -- I don't read what Moran did as saying that that didn't happen. I mean, he plainly says, yes, it did happen. And, so, what did he do with -- how do you think that he misread this article?

MS. O'DELL: Well --

THE COURT: Or study?

MS. O'DELL: -- I think in -- in a couple of ways.

THE COURT: Okay.

MS. O'DELL: Number one, he writes --

THE COURT: Are we still on 39?

MS. O'DELL: Yes, sir.

THE COURT: Okay.

MS. O'DELL: "Despite the contrary testimony from Dr. McCabe, Rose focuses on the media column -- his focus on the media column is logical. The blood in the media encountered the L1 virus-like particle only in the context of the three-dose vaccination. This pattern resembles what happened to Vanessia in a sense that no medical record suggests that she was exposed to the living strand of the human papillomavirus."

THE COURT: Mm-hmm.

MS. O'DELL: It's really not what this article -- it's a -- that is a misinterpretation of this article because the virus, if you will, is never an aspect of the Pinto article. It's always --

THE COURT: Right.

MS. O'DELL: -- the virus-like particle. And --

THE COURT: Okay. Well, I've been wrestling with this comment. And I'm trying to figure out precisely what he means here. I mean, it is true that there's no suggestion that she was ever exposed to the real thing.

MS. O'DELL: Yes, sir.

THE COURT: Her only exposure was through vaccinations.

MS. O'DELL: Correct.

THE COURT: And I think that's all he's saying. I'm not sure what inference he's drawing from it, but I think that's all he's saying.

MS. O'DELL: He says, and if we could go on, sir, he says, "If Vanessia encountered the human papillomavirus after the vaccine, the Pinto article predicts that she would have produced a robust immune response for the ones reported for 10 micrograms of the virus-like particle." That's --

THE COURT: Oh, those are micro, not milli, okay.

MS. O'DELL: Yes. So, that's not -- that's not the point of the article.

THE COURT: Mm-hmm.

MS. O'DELL: I mean, the conclusion of the article --

THE COURT: Well, I agree it's not -- it's certainly not the principal point of the article, but is it inaccurate to say that it would -- it would be consistent with the results of the article to say that if she was exposed to it that you would get a spike in the incidence of those virus -- would -- the immune response would spike.

MS. O'DELL: I don't believe that -- as I

understand it, after the three-course --

THE COURT: Mm-hmm.

MS. O'DELL: -- of the Gardasil vaccination, she -- or three-course -- three shots of a Gardasil vaccination, she would have an immune response to that.

THE COURT: Mm-hmm.

MS. O'DELL: But we're not talking about pro-inflammatory cytokines alone at that point. I mean, this study really was only to measure what the virus-like particle itself is doing in terms of generating pro-inflammatory cytokines. And really, sir, that --

THE COURT: Okay. I'm prepared to --

MS. O'DELL: -- I'm sorry. Go ahead.

THE COURT: -- I'm prepared to agree with it that this may not be directly relevant but I'm trying to figure out why it -- is it wrong. Or I guess what you're saying is missing the point of the article. But isn't he -- doesn't he concede the point that, yeah, if you do whatever they did, you're going to get this kind of elevated response?

MS. O'DELL: I don't believe --

THE COURT: Okay.

MS. O'DELL: -- that that -- I think by dismissing the stated conclusions in the Pinto article like he's done, I really read it that way. He says the Pinto experiment undermines the cohesiveness of Dr. McCabe or the Petitioner's

theory. And that's in part due to timing, and but also he is essentially saying that the media portion of this is the most important. And I guess, sir, just in terms of analyzing Pinto, that -- we view that to be arbitrary and capricious because there's no suggestion in the decision that Dr. McCabe lacked candor, wasn't qualified, wasn't an immunologist who knew what he was talking about.

THE COURT: Mm-hmm.

MS. O'DELL: I mean, and he -- yet after Dr. McCabe with his expertise explained what was going on in this -- these assays, and he has done these assays in the course of

his professional experience, these types of pro-inflammatory cytokine measuring, you know, studies.

And he explained what they meant and what they also mean in terms of the amplification process -- I'm going to talk about that -- and what that means for a patient who receives Gardasil like Vanessia, and in particular a patient like Vanessia, and we'll get to this, who is one of those individuals when confronted or receives a potent vaccine like this and as a result of the vaccine experiences this huge uptick in pro-inflammatory cytokines, but -- and our theory is Vanessia was a person whose innate and adaptive immune systems could not handle that assault and -- because that's what a vaccine is, it's an assault on the immune system --

THE COURT: Mm-hmm.

MS. O'DELL: -- could not handle that assault, and whereas the average girl would go back to balance after that --

THE COURT: Mm-hmm.

MS. O'DELL: -- she didn't. She went into what's called disregulation. That disregulation process is when essentially, as I understand it, it's like a loop in the immune system to continue to react, continue to react, producing pro-inflammatory cytokines, and that's when you get to the Mellins article and you see when those pro-

inflammatory cytokines are produced in a person with sJIA, then you get fever, rash, increased white blood cell count, et cetera.

So, you see, when you look at the Pinto article and its importance to the Petitioners' theory, it's central that the -- that it not be misinterpreted in the way that Special Master Moran did. And if you look at the article just a little bit further, sir, it talks about on page 5, it's -- that's what we've marked it, the page in the journal actually is 3559.

THE COURT: Yeah, I've got it.

MS. O'DELL: It talks about -- excuse me, let me make sure I've got -- it's essentially saying on the left side column, if you'll excuse me, sir, I lost my place here.

THE COURT: The highest increment in cytokine

response for whole blood cultures for vaccinated women relative to the month zero was observed following the injection of the second dose at month two for all cytokines measured. The greatest relative increases were seen for -- then he goes into the different things.

MS. O'DELL: The point being the greatest increase of pro-inflammatory cytokines was seen after shot number two. That's when the -- if you look at the table, that's when you see the greatest increase --

THE COURT: Well, when was that measurement taken? The one that's reflected in the table in this study? For example, the 10-microgram dosage for --

MS. O'DELL: It's -- the times are at zero, two months, and seven months.

THE COURT: Right. But, I mean, at two months, what they're doing is they're stimulating that sample. How quickly are they measuring?

MS. O'DELL: I believe it is almost immediately after that.

THE COURT: Right. I think it's almost simultaneous. That's the impression I had. And, so, then you get a spike. And then --

MS. O'DELL: And to continue with that, sir, once you get that spike, it goes back to what I was arguing, the -- in a person like Vanessia who we would argue is pre -- is

genetically predisposed to sJIA, there disregulation occurred in her situation, and that's what resulted in a onset of her sJIA.

THE COURT: Mm-hmm. Okay. I think I found where it was in this opinion that I was -- okay, I think on page 35 of the opinion, I don't know that you need it to -- all right, Dr. McCabe's theory includes two distinct proposition: first, the production of inflammatory cytokines can -- can

cause sJIA. That's really the conclusion. And, second, Gardasil can cause inflammatory cytokines. We've been talking about the second piece there.

I'm trying to figure out how much the Government concedes. Is the second piece of that contested? I guess I'm asking the wrong person, but that Gardasil can cause inflammatory cytokines or it can trigger the production or -- no, the activation or whatever of inflammatory cytokines. I don't think the Government disagrees with that.

MS. O'DELL: The Government, as I appreciate Dr. Rose's testimony, does not disagree that certain cytokines are involved in the, I'll characterize, sJIA, interleukin-1.

THE COURT: Well, that's the second half of it.

MS. O'DELL: Yes, sir.

THE COURT: The first half is whether or not the vaccine triggers the measurability of these innate cytokines, and my impression was that he didn't disagree with that. But

the second step, then, is to the extent the Government would agree with it, I think that sJIA is, to use your word, characterized by the presence of these inflammatory cytokines. And, so, what you've got is the logical syllogism, at least in part, is that these vaccines almost undoubtedly cause a spiking of the innate -- inflammatory cytokines, that's one; and, two, sJIA is characterized with,

associated with the presence of elevated levels of inflammatory cytokines.

And, so what you're asking -- and, number three, you're saying, therefore, sort of a post hoc ergo propter hoc, you're saying because of the vaccination you get the disease. And I think what Moran or Rose's argument was is that there's -- the link is missing. Yes, cytokines are produced; yes, they're present when you have the disease, but how do we know that one's caused by the other or that the disease is caused by the vaccine? I think that's what we're -- Moran is saying is the breakdown in the logic trail.

So, let me -- pardon the interruption to your progress, but did I misstate the Government's position with respect to the -- what it agrees with as to whether or not the vaccine triggers the elevated -- in layman's terms, triggers the elevated cytokine response, inflammatory, and, B, that those are associated with, characterized -- the disease is characterized by the presence of those?

MR. WISHARD: No, you didn't, Your Honor. I think Dr. Rose talked about that, that, you know, number one, pro-inflammatory cytokines have been involved in sJIA. Number two, vaccination --

THE COURT: Well, what does the word involve mean?

MR. WISHARD: I should not say involved, but

they've been noted in patients with sJIA. They may have some involvement in terms of producing sJIA symptomatology. And then the second point being that vaccinations, including Gardasil, and like many other things, that environmental stimuli can cause an elevation in pro-inflammatory cytokines. So, we don't disagree with those two points. And I think the third point, which I'll talk about when I get up, is there's a disconnect there.

THE COURT: Okay.

MR. WISHARD: In logic.

THE COURT: Okay. All right. So, back to your discussion about the article, what's -- what's the best that can be drawn from the Pinto article. Forget about what Moran did with it, what do you think he should have concluded from it?

MS. O'DELL: I think he should have concluded that following each vaccination with Gardasil there is a intense and increasing elucidation of pro-inflammatory cytokines.

THE COURT: Okay, now, hang on a second. The

article doesn't literally say that, because it draws a distinction between -- I mean, you have to -- you'd have to draw an inference to say that it's the vaccination, because the really spike response comes from taking the stuff, the blood sample, and administering the -- what do we call these

-- VLPs or something?

MS. O'DELL: Virus-like particles.

THE COURT: Directly into the Petri dish.

MS. O'DELL: Yes, sir.

THE COURT: It's not a, quote, vaccine, per se.

MS. O'DELL: But that is the virus-like particle that is the primary portion or primary makeup of Gardasil.

THE COURT: Oh, yeah, I understand.

MS. O'DELL: So --

THE COURT: But, I mean, the way they're doing it is not in the traditional stick-a-needle, I just got my flu vaccine 30 minutes ago. It's not a needle in the arm. It's directly injecting 10 micrograms or one microgram right into the sample, right?

MS. O'DELL: Yes, sir, that's correct.

THE COURT: Okay. And then you said -- what was the phrase you used, significantly -- and increasing.

MS. O'DELL: Intense and increasing.

THE COURT: And by increasing, do you mean over time but if a third dose?

MS. O'DELL: Yes, sir.

THE COURT: Okay.

MS. O'DELL: What you see is if you look at 10 micrograms, for example, which is the second column.

THE COURT: Mm-hmm.

MS. O'DELL: If you look and it's got L1 10 micrograms and then vaccine versus placebo, and you look, for example, at IL-6, interleukin-6, you're showing a steady -- you know, you've got, you know, 44.9 --

THE COURT: Mm-hmm.

MS. O'DELL: -- at the first dose or zero; then you have 1135.7, you know, huge increase after the second month; and then after the seventh month, you have a -- it's not as large as after the month number two, but after the seventh, you have continuing intense production of pro-inflammatory cytokine.

THE COURT: Okay. Take all that as a given. Whatever's here is here. I don't think my reading of the Special Master's decision doesn't say I don't believe the results. He's got to cope with the results. And, so, let's assume that the results are the results. How does it get you past -- how does it bridge the, and therefore caused, as opposed to is present at the scene of the crime kind of analysis?

MS. O'DELL: When you look at -- and let me just

back up and say it's a hard question.

THE COURT: Yeah.

MS. O'DELL: I mean, there's no -- there's no -- if

there was a medical article that said it, we would have, you know, brought it to the Court's attention.

THE COURT: Right. Right.

MS. O'DELL: So, it's a hard question, but when you look at this, what Pinto could be relied on to say is this -- these -- the ways in which these particular pro-inflammatory cytokines reacted and is represented in Table -- Table 1 of this article, is evidence of what was happening in Vanessia, even though --

THE COURT: Okay.

MS. O'DELL: -- in a patient pro-inflammatory cytokines are never tested. I mean, you don't go to the hospital and when they -- you have fever they test you for what pro-inflammatory cytokines, you just -- that didn't happen.

THE COURT: Right, okay.

MS. O'DELL: So, this is from our standpoint evidence that what's happening in this table or 10 micrograms is essentially a picture of the pro-inflammatory cytokine response in patients who've had Gardasil.

THE COURT: Okay. Take all that as a given --

MS. O'DELL: Is that helpful?

THE COURT: Oh, it is. And I don't -- I don't think he's quibbling, he Moran or Rose, and I guess Rose is

the more relevant one, with that, that it's --

MS. O'DELL: But he --

THE COURT: -- that using the manipulation of the cultures or the samples is analogous to what's going on if you actually give somebody -- what I didn't see is 10 micrograms in a volume, if it's a test tube or whatever. I mean, is that -- how do we know how that compares to the percentages of somebody who weighs 100 pounds getting an injection? I mean, do we know anything about -- does the article say anything about that?

MS. O'DELL: No.

THE COURT: Right.

MS. O'DELL: It is not specific in the patient. It is really because inside, as I appreciate it, that type of testing in a live patient is not possible. This is the state-of-the-art way to try to measure pro-inflammatory cytokines over the course of a -- a vaccination course.

THE COURT: Okay. So, what we get is step one in the logic train is this and other evidence suggests that, and the Government doesn't really contest that, you get a potentially dramatic response, in fact, it's kind of hoped for and expected dramatic response, in terms of the innate cytokines when you get the vaccine. And then we look at

people that have sJIA, and they have increased levels of

these same kind of pro-inflammatory cytokines.

MS. O'DELL: Yes, sir.

THE COURT: And, well, I don't mean to be dismissive, but, I mean, is that it? I mean -- it can't help but sound dismissive. It's not meant to be. I understand we're dealing with limited -- we're dealing in the vaccine world and we're dealing with I won't call it a lower standard of proof, but we're dealing with something -- a sympathetic program. And, so, we're sympathetic to the fact that there's not going to be a lot of hard evidence. But, what it boils down to --

MS. O'DELL: So far it hadn't felt very sympathetic. I will say that.

THE COURT: Well, okay.

MS. O'DELL: Not from you, Your Honor.

THE COURT: Okay.

MS. O'DELL: I'm referring to Special Master Moran. Let me talk about sJIA, then.

THE COURT: Okay.

MS. O'DELL: Just -- and, you know, I think the two best articles in the record in this case, and I've actually learned of others since this case was tried and the record really was closed, but the Prakken article and the Mellins article. And those are Exhibit 12, I believe, and Exhibit

13. And, you know, if we could start with Prakken, and he, large measure, Special Master Moran dismisses both Prakken and Mellins, and particularly Mellins as being hypothesis-generating and not -- and not substantive. And we believe that that was an arbitrary and capricious finding.

And starting with Prakken, which was published in The Lancet, I mean, a premier journal, and it's new research, it's not an old article. It was published in 2011. And Dr. Prakken says a couple of things there talking about -- they talk about environmental triggers in this article on page 4 -- page 4 of the exhibit, it's page 2141 of the article, it talks about vaccines being potential triggers of idiopathic arthritis. And you'll see that there, Your Honor, on --

THE COURT: Right.

MS. O'DELL: And it doesn't -- it's not conclusive. It doesn't say they do. It says they are -- it says self-perpetuating loop of activation of both the innate and adaptive immunity that cause tissue damage, that's the disregulation I talked about --

THE COURT: Mm-hmm.

MS. O'DELL: -- that occurs.

THE COURT: Well, where are you -- you're in column -- on the left column?

MS. O'DELL: Yes, sir, let me -- and let me just go up a little bit. It says --

THE COURT: Oh, I see it.

MS. O'DELL: It says, "Much the same as with most human autoimmune diseases, the cause of juvenile idiopathic arthritis is assumed to be multifactoral. A genetically susceptible individual might develop a deleterious and uncontrolled response toward a self antigen on exposure to an unknown environmental trigger. This response causes a self-perpetuating loop of activation of both the innate and adaptive immunity that causes tissue damage in juvenile idiopathic arthritis. Infections and vaccines have been suggested as to candidate triggers."

THE COURT: Okay. He quotes that in his opinion. And I think -- I mean, what he says is correct, "has been suggested" doesn't mean that these people -- or I guess this individual, yeah, no, it's three of them -- are saying we tested for that or in other words, other people are saying or speculating these might be legitimate places to look.

MS. O'DELL: They say they haven't been confirmed because of the scarcity of proper controlled perspective studies.

THE COURT: Right.

MS. O'DELL: And for sJIA, Your Honor, the incident rate for sJIA is, Dr. McCabe testified, two in 100,000. In a reference that Dr. Rose put in the record, it's as low as .6/100,000. There would have to be huge, you know, in the

millions, in an epidemiological study to test some of these as triggers and get a statistically significant conclusion.

THE COURT: Mm-hmm.

MS. O'DELL: And, so, there is a need for epidemiological studies, but because of the rarity of sJIA, the data is not available because of the cost of the studies, et cetera.

THE COURT: But if -- but how could this be affirmative evidence of anything? I mean, in effect, these guys are saying we think some people are genetically predisposed, and if you have the right trigger it may trigger a dramatic response, including development of the disease. Aren't they in effect saying this is -- it's a plausible hypothesis that needs to be explored?

MS. O'DELL: They are saying -- I think he goes on -- it's more than that.

THE COURT: Okay.

MS. O'DELL: I mean, if you look at page 5 of the article, the next page, they're saying environmental triggers cause sJIA. I mean, I think that's the import, if you look at Figure 1, where you see on the left side that middle of the figure, it says environmental trigger.

THE COURT: I'm sorry, this is in the diagram?

MS. O'DELL: Yes, sir, environment.

THE COURT: Okay. Right.

MS. O'DELL: And it shows --
THE COURT: Right, but I mean --
MS. O'DELL: Well, and --
THE COURT: -- what about peanut butter, I mean, or, you know, wearing seatbelts in a car?
MS. O'DELL: And my point being, sir, that I'm not saying and we're not arguing, the Petitioner is not arguing that Gardasil always causes sJIA.
THE COURT: Mm-hmm.
MS. O'DELL: That's not -- that's not our argument. Our argument and -- and this is what Prakken is saying, in a context of sJIA, a person who does have that genetic disposition, it doesn't mean -- if a person has a genetic disposition, it doesn't mean they're going to get a condition.
THE COURT: Mm-hmm.
MS. O'DELL: In other words, you can have the BRCA1 --
THE COURT: Right.
MS. O'DELL: -- you know, gene and still not get breast cancer. It's not a foregone conclusion. But in certain predisposed individuals and an individual predisposed for sJIA, if there -- an environmental trigger causes this disregulation, whereas in the, I won't call them normal, but other --

THE COURT: Mm-hmm.

MS. O'DELL: -- patients their immune system would go back, the adaptive and innate immune systems would go back to balance.

THE COURT: Right.

MS. O'DELL: And, so, our theory is that Gardasil that provokes this intense and lasting generation of pro-inflammatory cytokines is really -- is what you're seeing happen in this figure is that there is -- there is genetic susceptibility, but once that trigger happens there's the release of the pro-inflammatory cytokines that causes disregulation, in other words, the system really just goes into a flurry, to use a layperson's --

THE COURT: Mm-hmm.

MS. O'DELL: -- but it didn't stop; it's perpetuating.

THE COURT: No, I understand the theory.

MS. O'DELL: And that's what causes the tissue damage, yes, sir.

THE COURT: Right.

MS. O'DELL: But --

THE COURT: I mean, let's assume it's a plausible theory that needs testing. Well, I have to abstract myself away from what I would do if I was the trier -- the initial trier of fact, as it were. What I'm faced with is the

Special Master's having considered that and coming to a conclusion that the proof isn't there.

You could have a plausible theory and at least not given the state of the art as it were of sufficient proof. And, so, do you not have to show -- well, this is what you've obviously been trying to do, that it was -- the decision was arbitrary and capricious because no reasonable person could have come to that conclusion.

MS. O'DELL: We would say that it was arbitrary and capricious because it really required us to put forth scientific certainty, I mean, an article, essentially that says Gardasil in susceptible individuals causes sJIA. That study will never be done by virtue of the fact that sJIA is such a rare -- I mean, such a rare disease.

THE COURT: Mm-hmm.

MS. O'DELL: And, so, we feel like that's where the Special Master put us, is holding us to a standard by saying your theory is not peer-reviewed. Well, we believe that that's unfair because the articles that support the cytokine production as a -- is -- they are well regarded, peer-reviewed --

THE COURT: Mm-hmm.

MS. O'DELL: -- real scientists. I mean, not --

THE COURT: Mm-hmm.

MS. O'DELL: -- they're not on the fringe. They

are at the -- I mean, Ian Frazer and the Pinto group, I mean, he's probably getting the Nobel Prize for what he's done with the VLP. I mean, this is significant. And then you look at -- I've talked about Prakken; I'd love to talk about Mellins. And we've got a -- this is not sort of, you know, cheap science.

THE COURT: Oh, I understand.

MS. O'DELL: I mean, this is The Lanset.

THE COURT: Right.

MS. O'DELL: I mean, it's significant. And, so, we feel like he held us to a standard of scientific certainty in the way that he analyzed the evidence, because if outlining a logical theory and a theory that's not only plausible but it's supported -- I mean, each aspect of our theory is, we would say, substantially supported in the literature. And, now, can we show -- and we believe that's -- we've laid out a logical theory. Can we point to an article that's going to make, you know, that connection?

THE COURT: Mm-hmm.

MS. O'DELL: No, sir, we can't. I mean, it's not in the literature. It hasn't been studied. But we don't view the burden of proof under the Vaccine Act to require that. And we --

THE COURT: One thing that you take issue with, in effect, Special Master Moran's -- let me see if I can recall

some of the criticisms. I understand what you're saying, and I agree it's an issue.

MS. O'DELL: I can move forward, sir, if you want me to go through some of my criticisms.

THE COURT: Oh, yeah, you're welcome to. And I'm not trying to short circuit anything. Let's see. For example, well, like the animal studies, I don't remember exactly what it was or what Special Master Moran did with that, but in effect he's saying there's no animal studies. And you criticize him for that -- or maybe no epidemiological studies that actually draw that -- bridge the synapse there.

MS. O'DELL: Yes, sir. Let me -- sorry.

THE COURT: But one way to read his opinion is saying if we have that stuff, it would be highly relevant and I would certainly consider it. And he goes through a list of things that aren't there, in effect. There's no animal studies; there's no epidemiological studies that actually draw the specific link.

And then you come to the conclusion that he's set an unmeetable standard. And I agree that is potentially -- I don't mean this particular -- opinion in particular, but that's something that we have to make sure doesn't happen. But by the same token, how can we go through the evidence without saying -- looking at the logical places and saying

they're not there, that doesn't necessarily mean that he's

saying, or does it, I'm requiring something like that as proof.

MS. O'DELL: Yes, sir.

THE COURT: I mean, I think he's trying to give you some benefit of what's out there and testing it and seeing if it satisfies the proof, but I don't know that it's fair to say that what he's doing is saying I have to have it in order to agree with you. I'm not -- that may be a bit of a leap.

MS. O'DELL: I think -- let's take up the epidemiological studies.

THE COURT: Mm-hmm.

MS. O'DELL: I mean, Chao and Verstraeten. Special Master Moran does state they're not required.

THE COURT: Mm-hmm.

MS. O'DELL: Epidemiological evidence is not required.

THE COURT: Right.

MS. O'DELL: I would suggest to the Court that those are sort of magic words more than --

THE COURT: Yeah, but how can he look at Chao and critique it? I mean, he's got to look at Chao and he's got to critique it if somebody puts it in front of him. And the fact that he says, well, this isn't proof, to bridge that

gap, is that the same thing as saying I'm requiring it as proof?

MS. O'DELL: I think he used Chao and Verstraeten -- and they're very different --

THE COURT: Mm-hmm.

MS. O'DELL: -- you know, and that he used the results in those articles to support his conclusion that our theory was not true, you know, or --

THE COURT: Well, how do you --

MS. O'DELL: I mean, that's how I view that --

THE COURT: -- how do you move from -- I can't remember who put what in front of him. Verstraeten the Government put in front of him, right?

MS. O'DELL: Right.

THE COURT: And Chao?

MS. O'DELL: We did.

THE COURT: Yeah, on the timing issue or --

MS. O'DELL: To -- well, and to explain --

THE COURT: Okay.

MS. O'DELL: -- timing in part, but to explain that it's out there, it's an epidemiological study, it involves Gardasil. But here the reasons it's not relevant to the facts in this case --

THE COURT: You said that?

MS. O'DELL: That's my -- our position.

THE COURT: Right. And you had to, in effect, distinguish in part because it came to the conclusion that

there's no cluster of disease onset in relation to vaccination timing, blah, blah, blah. But, I mean, how -- he's got to deal with it. He's got to critically analyze it. And, so, how can you do that without getting tarred with the brush of, ah, you're setting up a test for us that's impossible to meet?

MS. O'DELL: I think in part, it's a 56 -- 56-page opinion, and he spends 10 pages on the epidemiological. I mean, and that's not the whole reason, but, I mean, he goes through them in such a way that he uses the conclusions to, I believe, support his finding that our theory is unpersuasive and -- or -- and --

THE COURT: Well, from the Government's perspective, they're entitled to do -- to critique your causation theory by putting in their own evidence. And can he pay attention to it if it's persuasive, if that contrary evidence is persuasive?

MS. O'DELL: I mean, he -- yes, sir.

THE COURT: Okay.

MS. O'DELL: He can take that in consideration. I'm not saying that he can't. But let's take Verstraeten,

for example. To -- Verstraeten is a different vaccine.

THE COURT: Right.

MS. O'DELL: It's different adjuvant.

THE COURT: Well, okay, but -- all right, but

consider what would have happened. Suppose we had two other vaccines, not whatever the two were that they looked at there, and you get a direct causal connection to HP -- or whatever, to sJIA.

MS. O'DELL: sJIA, mm-hmm.

THE COURT: Would you not offer that as some indication as analogous evidence that, yeah, there's a connection here?

MS. O'DELL: I mean, the -- I would certainly do that.

THE COURT: I would assume so. And, so, is it not fair to say the reverse? I mean, to in effect say analogous studies haven't suggested a connection, if that's in effect what Verstraeten is saying? Of course, now, Verstraeten is looking at a totally different conclusion. I mean, he's testing against measles, mumps, and whatever. He doesn't deal with --

MS. O'DELL: No. No, sir, that's actually the Cervarix study, sir, Verstraeten is. The two epidemiological studies, Chao -- Chao deals with Gardasil --

THE COURT: Oh, right.

MS. O'DELL: -- and that's, of course, HPV vaccine. And the other HPV vaccine study is Verstraeten. And that's dealing with Cervarix, which is GlaxoSmithKline's HPV vaccine. And this has --

THE COURT: Okay.

MS. O'DELL: -- and our point with those, Your Honor, is let's take the joint criticisms I would have, is neither study had as a primary endpoint sJIA.

THE COURT: Mm-hmm.

MS. O'DELL: So, you've -- they had JRA.

THE COURT: Mm-hmm.

MS. O'DELL: And you can argue that some subset of JRA in terms of ICD-9 codes, and the Government has done this, has said some subset of JRA, you know, patients, because it's the same ICD-9 code, are sJIA. We have no evidence of what that is or if there are any in these studies. So, we just say the conclusions themselves are -- should not be --

THE COURT: Affirmative evidence.

MS. O'DELL: -- that it does not cause sJIA because the endpoint is not appropriate. Second, for neither study, the power, the number of patients necessary to show a statistical result for sJIA, both studies are inadequate.

THE COURT: One of them had 180-some-thousand.

MS. O'DELL: 189,000.

THE COURT: Yeah.

MS. O'DELL: 68,000, I believe, in the Verstraeten, the Cervarix study, but for a disease that has a instant rate -- incident rate of two out of 100,000, you would need more

than a million individuals in that study in order to draw statistically significant conclusions about sJIA.

THE COURT: Mm-hmm.

THE COURT: Mm-hmm.

MS. O'DELL: It's just very rare. So, you look at those two studies and sJIA is not an endpoint; the power is not present for either -- for sJIA purposes is not present in either study; and then you've got the Verstraeten study being -- involving a different vaccine, adjuvant, et cetera.

So, we just feel like that Special Master Moran said epidemiological evidence is not required, then they looked at those two particular studies and said they didn't -- neither one showed an increase in sJIA, and that undermines the Plaintiffs' or the Petitioners' theory.

THE COURT: It certainly doesn't support it. Now, I'm trying to -- this is sort of radioactive stuff in terms of I'm sympathetic with anybody having to argue from these things. Plainly it would be fair to say they don't support a

causation theory as a direct study of any kind --

MS. O'DELL: They --

THE COURT: -- for the reasons that you've outlined.

MS. O'DELL: Yes, sir.

THE COURT: Now, is it fair to say that if they had a whiff of support for the Plaintiffs' theory because the

results were different that the Plaintiff would say they're not on point but they're analogous, we're talking about a similar vaccine or we're talking about a similar disease or a similar whatever, and you get -- there's a -- we're satisfied there's a connection to these analogous theories, I mean, analogous studies are used routinely. You'd be arguing from them. And, so, here what we have is analogous studies -- they're similar but they're not similar enough, and in any event, the results wouldn't help the Plaintiff. What's wrong with that?

MS. O'DELL: If the studies themselves as we suggest are not relevant for all the reasons I've outlined --

THE COURT: Mm-hmm.

MS. O'DELL: -- I mean, that -- those differences are real.

THE COURT: Mm-hmm.

MS. O'DELL: And, so, for purposes of sJIA, they

are not relevant, so their presence shouldn't be used -- I mean, if they're not required and they're out -- these studies are out there and we view them not to be relevant at all, the Special Master should -- it's inappropriate, we believe, for the Special Master to make a finding, well, those -- those are in the negative column for you, Petitioner, which is where I felt he put them. And then he -- because he quote Verstraeten in particular at length.

THE COURT: Mm-hmm.

MS. O'DELL: And to say, you know, essentially -- the quote that comes to mind is --

THE COURT: Where are you?

MS. O'DELL: Page 56. I mean, he just uses in a broad way to say causation and coincidence might be confused, and then he quotes, and he says, "the broader use of HPV vaccines and other vaccines targeting this age group, autoimmune disorders will be reported and temporal association with vaccine administration, even in the absence of causal relationship." I just don't think that's -- that's just not a fair conclusion.

THE COURT: Well, okay, I remember that from -- maybe not just from this. Somebody else said that, too, that -- maybe it was Chao. They said there's going to be background development of sJIA in any population, and yet --

I mean, I gather part of this is we don't want the baby thrown out with the bath water. We want to keep administering this human papillomavirus vaccine.

And, so, we don't want the fact that somebody gets arthritis to keep -- you know, suddenly cause a panic and everybody -- and so we're going to test to see if there's a connection. And in the process of teeing that question up, I think both Chao and Verstraeten say, in effect, the same thing, because you've got this background level of the

incidence of juvenile rheumatoid arthritis, idiopathic --

MS. O'DELL: Sir, can I just say?

THE COURT: Yeah.

MS. O'DELL: Which is very different. You know, if you think of the overall big tent juvenile rheumatoid arthritis, then you've got sJIA, which is a very different disease, and you could argue many cases and much more serious and there's a subset. But, so, just sJIA was not a part of the consideration for Chao or Verstraeten.

THE COURT: Okay.

MS. O'DELL: I'm sorry to interrupt you, sir.

THE COURT: I stand corrected. But I need to go back and read precisely what it is that they're identifying as sort of the background noise of disease. But, I mean, it' a fair -- this -- you could have a study that's utterly

irrelevant and it could by accident state a fact that everybody recognizes is true. Right?

Well, you don't have to agree with that. I think it would be the case. I mean, it would be perhaps totally serendipitous, but you could have something -- a study in the vaccine area about some other vaccine and they could make a statement about the Gardasil vaccine that might be accurate. Right?

MS. O'DELL: Yes, sir.

THE COURT: And, so, the question that I would

raise about his quotation here is, is he looking at the results, or is he simply referring to that sort of background data?

MS. O'DELL: I mean, you could argue he's referring to the background data. I just think if you look through the totality of his decision --

THE COURT: Mm-hmm.

MS. O'DELL: -- and the amount of emphasis he placed on those studies, it suggests that though he said epidemiological evidence was not required --

THE COURT: Mm-hmm.

MS. O'DELL: -- when he evaluated them, he -- I think his analysis of those studies was that they -- they show that those vaccines don't cause arthritis, even though

neither one of them had sJIA. I mean -- let me back up.

His analysis was that neither one of those studies support a finding that those vaccines cause sJIA, and I believe --

THE COURT: Well, hang on. Is that accurate?

MS. O'DELL: He did not write those words in sum.

THE COURT: Okay.

MS. O'DELL: But that's my -- that is -- would be the Petitioner's interpretation of the way --

THE COURT: Okay. But, I mean, if he had said it, would that be accurate, I guess, is my question.

MS. O'DELL: Of the articles themselves?

THE COURT: Mm-hmm, right.

MS. O'DELL: We can't know that, because sJIA was not a --

THE COURT: Okay.

MS. O'DELL: -- was not an endpoint.

THE COURT: Right, fair enough. Right.

MS. O'DELL: I mean, you could argue, and I'm sure that Mr. Wishard will, that the ICD-9 codes that they were focused on these, you know, epidemiological studies --

THE COURT: Were generic or --

MS. O'DELL: -- were that larger group.

THE COURT: Right.

MS. O'DELL: And there may be some sJIA people in there. But we don't have any information that there were or there weren't.

THE COURT: Right. But, I mean, how does a special master cope with the fact that you start casting about in all these directions looking for something that might give you a clue and you look at something that's analogous and say, well, there's no proof there? That could be true, and it might be subject to the criticism, well, aha, he's saying it had to be true for us to recover. He may not be -- have actually had that in mind. He's just stating a fact that the study doesn't -- is not direct proof of what's useful here.

Anyway, I don't mean to belabor that point, but --

MS. O'DELL: No, sir, not at all. And if you'll give me just a moment, sir. Maybe I'm not being very helpful to you, and I apologize.

THE COURT: Oh, quite the contrary.

MS. O'DELL: Let me just ...

I mean, he -- in his first -- he analyzes these studies essentially on three occasions: pages 8 through 11.

THE COURT: Mm-hmm.

MS. O'DELL: And he goes through the conclusions, and he basically says, you know, for the Chao article, they did not make specific findings for juvenile arthritis. Their

overall conclusion essentially was, you know, there's no increase, there's no statistically significant increase of JRA. Essentially the same conclusion in Verstraeten. And if you'll look again, sir, on page 29 through 32 -- excuse me, 30.

THE COURT: Okay.

MS. O'DELL: He talks again -- he reviews this in the context of Dr. Rose's testimony about Chao, and then if you'll go further, sir, 42 through 44 --

THE COURT: Oh, there's no question, he spent a lot of time talking about him.

MS. O'DELL: No -- yes, sir. Then he --

THE COURT: But wouldn't -- would the decision have

been any stronger if he'd just said, well, those studies are not on point? Would it have been any less subject to attack? I mean, if so, then what you're -- what we're reduced to is we have A, we have B, and therefore C. And he's saying you can have A and you can have B, but that doesn't necessarily mean you got C.

MS. O'DELL: Well, maybe this is the way to describe it, sir. When he -- this is -- page 44 may be the best. He says, "The Verstraeten and Chao articles are additional but not decisive reason" -- excuse me --

THE COURT: Mm-hmm.

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MS. O'DELL: -- "an additional but not decisive reason for finding that Dr. McCabe's theory that the vaccine against human papillomavirus can cause sJIA to be unlikely."

THE COURT: Mm-hmm.

MS. O'DELL: The same result would have occurred even if the -- the epidemiological studies were not a part of the record. It just -- he says those words there. But when you look at the totality of the decision, he -- what the law says is not required, he's looked at, we've pointed out all the reasons that those studies have limited relevance. I would actually argue Verstraeten, in this circumstance, is not relevant.

You know, maybe I'm taking the most narrow view of Verstraeten, but the -- and he's saying those basically weigh

against the Petitioner. And we feel like if the law is epidemiological studies shouldn't be required and there are two studies out there and -- and we can say they don't show a statistically significant increase of JRA, I don't dispute that. That's what those studies say. I can dispute their design, I can dispute a lot of things, but I don't dispute that that's what the published articles say, both of which, by the way, are funded and paid for by the manufacturers, you know, but that's --

THE COURT: Mm-hmm.

MS. O'DELL: -- not something we get to explore here. So, I'm not disputing that's what they say, but then to take those conclusions, even when the -- on cross examination of Dr. Rose and in the testimony of Dr. McCabe we pointed out all the ways that those should be set aside, for him to take those and say, hey, that -- that makes their theory unlikely.

THE COURT: Mm-hmm.

MS. O'DELL: I think that's unfair and that's -- that's putting us in a place of if not scientific certainty, something above what I think the vaccine law requires. So --

THE COURT: Mm-hmm.

MS. O'DELL: -- that's the -- that's the crux of our argument on epidemiological studies.

THE COURT: Mm-hmm.

MS. O'DELL: Sir, can I just point out another area that is just troubling and we believe to be error? And it relates to Dr. Moran's analysis of the MMR study involving --

THE COURT: You said Dr. Moran. Did you mean the Special Master or Dr. Rose?

MS. O'DELL: I'm so sorry. Special Master Moran.

THE COURT: Okay.

MS. O'DELL: Yeah. If you'll turn, sir -- let me make sure I'm on the right page here. He analyzes on --

beginning on page 36, the Hedgestack and the Zonneveld articles.

THE COURT: Mm-hmm. Oh, much a Dutchman, or maybe Heijstek is Norwegian, I think, isn't he? Okay.

MS. O'DELL: Haystuck? Is that how you pronounce it, sir?

THE COURT: I don't know, Heijstek, I guess. Maybe you're right. Okay.

MS. O'DELL: I may -- I think I've just given it the South Alabama pronunciation. But here -- let me just -- this is another criticism, that he -- he relied -- he states that these articles are more relevant than the articles put forth by Petitioner. In other words, he discounts -- let me make sure I'm to the right language, sir.

THE COURT: Okay.

MS. O'DELL: He says -- and he's comparing these

articles to others that the Petitioners put forth. And if I'm not mistaken, it's the --

THE COURT: Well, these were -- these were offered by -- is it Rose?

MS. O'DELL: No, sir. Here's how these came about. In the Prakken article, and, sorry, I lost my sort of train there for a second.

THE COURT: Oh, well.

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MS. O'DELL: But I'm back on track. The Prakken article, which talks about juvenile idiopathic arthritis and the development of that, and he cites the -- Dr. Prakken cites in his article these two studies, the Haystuck study and Zonneveld study that were Exhibit 43 and 47. Those were not studies that were put forth by either party prior. On the prehearing -- during the prehearing call, Special Master Moran asked the Petitioner to put those studies in the record. And of course we were happy to do that on his request.

And then in the -- talking about whether our theory, you know, has been tested that Gardasil can cause sJIA, and of course we've been talking about theory -- Pinto primarily -- and then Prakken, and then he focuses on these two articles and essentially says Plaintiffs' articles are theoretical; these are more relevant.

And -- and, so, in doing that, sir, we believe he

-- he really -- it was an unfair --

THE COURT: Here it is on page 37, because these are studies, the Heijstek and the Zonneveld findings are entitled to more weight than the speculative passages in other articles.

MS. O'DELL: Yes, sir.

THE COURT: Okay.

MS. O'DELL: And we feel that that improperly elevated the burden of proof. And just the Heijstek article is -- deals with the MMR vaccine. It's a mixture of live viruses. It has a different adjuvant than Gardasil. It's -- it doesn't produce the same potent response to measles, mumps, and rubella in the same way that Gardasil does for the human papillomavirus, more than 100 times the natural infection.

You know, the patients in the Heijstek study, they had JIA. This wasn't about cause. It was --

THE COURT: Mm-hmm. About aggravation.

MS. O'DELL: -- aggravation with their own therapy. You know, it is just not a study that should be used to say we're going to -- I'm going to dismiss what Petitioners' expert, Dr. McCabe, puts forth, even though he's an immunologist, I don't believe that Dr. -- excuse me, that Special Master McCabe [sic] at any point questioned his candor, questioned his --

THE COURT: Oh, I agree.

MS. O'DELL: -- you know --

THE COURT: Yeah. In fact, I think he discounted -- apparently both of you all questioned, challenged on bias grounds each others' witnesses, and he says that he didn't give that any traction.

MS. O'DELL: So -- but in terms of these studies, it doesn't measure -- the Heijstek study does not measure pro-inflammatory cytokines. It is just a very different study. And then to say, you know, this is --

THE COURT: Well, he's saying in different in kind. I agree that the results may be very non-analogous potentially, but he's saying it's different in kind. One was actually a study and one was a we need to do more research because there's a possible connection here kind of statement.

MS. O'DELL: Yes, sir, that's right, but then he -- but to take these studies and say to the extent the differences can be overlooked, and our point -- and this is what he writes, the Heijstek study and the Zonneveld-Huijssoon study suggests that when researchers had explored whether vaccines affect juvenile idiopathic arthritis, they have not found that the disease worsens -- the vaccines worsen the disease. And because they are studies --

THE COURT: So, he's giving it some credence.

MS. O'DELL: Entitled to more weight than -- than

other speculative passage in -- excuse me -- more weight than speculative passages in other articles.

THE COURT: Mm-hmm.

MS. O'DELL: And -- and we believe that that is arbitrary and capricious to hold that out, which is so

distinctly different from Gardasil. And in relation to the Heijstek study, essentially Special Master Moran criticizes Dr. McCabe for -- in a sort of subtle way, but he criticizes him for not knowing whether the MMR vaccine increases cytokines. Well, the study didn't test for cytokines.

THE COURT: Mm-hmm.

MS. O'DELL: And then the -- in terms of the meningococcal C vaccination, Dr. McCabe testified that meningococcal C vaccination does not increase pro-inflammatory cytokines, period. So, it's just a very different setting. And to -- and, of course, that MC vaccine is against -- is a -- it vaccinates against a bacterial infection, not a viral infection, has different adjuvants. We feel like by placing emphasis on those studies and discounting the Petitioner studies was -- was improperly raising the burden or holding us --

THE COURT: Who came up with Prakken?

MS. O'DELL: Petitioner.

THE COURT: Okay. Did the two experts have the opportunity to consider these articles?

MS. O'DELL: He -- the Special Master asked Dr. McCabe questions about these articles when he asked him questions. So, they certainly were in the record. I think that he asked general questions to Dr. Rose about the

meningococcal C vaccine, but I don't recall him going into detail about the studies themselves.

THE COURT: Well, were these two studies already part of the record at that point, or did he have them brought in later?

MS. O'DELL: They were brought in before -- just prior to the hearing.

THE COURT: Oh, okay. All right.

MS. O'DELL: He requested them during a prehearing telephonic conference.

THE COURT: I see. Okay.

MS. O'DELL: And, so, we feel like that was inappropriate. When you go further, Your Honor, and you look at other aspects of the Special Master's opinion, and one in particular relates to the Mellins article. He dismisses the Mellins article.

THE COURT: Well, didn't you say y'all didn't spend a lot of time -- by you all I mean both sides -- didn't spend a lot of time talking about it?

MS. O'DELL: No, sir. I think that was another one.

THE COURT: Oh.

MS. O'DELL: This was a -- this is an article that talks about the manifestations of pro-inflammatory cytokines

--

THE COURT: Mm-hmm.

MS. O'DELL: -- in juvenile idiopathic arthritis.

THE COURT: Okay.

MS. O'DELL: In the decision, and this is Exhibit 13. In the -- this was put forth by the Petitioner. And the title of the article is "Some Answers, Some Questions -- or More Questions."

THE COURT: Oh, yeah. I remember this, okay.

MS. O'DELL: And he draws into question the validity of the conclusions in this article by saying, you know, it's a hypo -- hypothesis generating. That's what Dr. Rose said about it. And we're not saying that there are not questions that are raised in this article that aren't answered. This is not the definitive text on --

THE COURT: Mm-hmm.

MS. O'DELL: -- you know, JIA. That's not the point. We put forth this article to show that when disregulation occurs and sJIA is manifested in a individual like Vanessia, if you'll look on page 4 of the article, you'll see a figure that is, frankly, more complicated than I can speak to in detail. But when -- if you look at the upper

portion of the figure, you see TLR and IL-18R.

THE COURT: Mm-hmm.

MS. O'DELL: Do you see it?

THE COURT: Mm-hmm.

MS. O'DELL: And this is the feedback loop, as I understand it, the disregulation for pro-inflammatory cytokines. And that --

THE COURT: What does TLR stand for?

MS. O'DELL: Toll-like receptor.

THE COURT: Toll, T O L L ?

MS. O'DELL: T O L L. Toll-like receptor.

THE COURT: Okay.

MS. O'DELL: And you see this feedback loop, so you got, you know, information being provided basically in both direction from cells. And if you'll look, you'll see that IL-6, TNF, and then you'll see IL-1 and IL-18, that those are the pro-inflammatory cytokines that are implicated in systemic juvenile idiopathic arthritis. That's not in dispute. Dr. Rose agrees with that.

And then if you'll look down, this is the important part, he dismisses Mellins as hypothesis-generating, more -- you know, some answers, more questions, but the purpose for which the Petitioner put this forward -- this article forward is this concept that when there is -- in sJIA, when you have this disregulation, it's perpetuating, it's ongoing. And

these pro-inflammatory cytokines are being elicited in large

measure. What you get are clinical manifestations.

So, if you work your way down to the figure and you see the tissue factor, vascular permeability, white cell -- white blood cell recruitment or increase in white blood cells, fever, acute proteins or like-C reactive proteins, for example, common myeloid progenitor, and then synovial inflammation or, you know, redness in the joints. All of those are clinical manifestations that are present in Vanessia. I mean, you see this -- those are evidence of the increase in pro-inflammatory cytokines.

And, so, we feel like this article was unfairly dismissed for the -- because -- for the purpose we put it forward I'm not sure that there is dispute and, so, it's -- for Prong Two of Althen, if we worked our way through Prong One of basically what I call general causation, a logical theory, and then you get to specific causation, this article becomes very important because --

THE COURT: But isn't it useful -- well, wouldn't it be useful from the Plaintiffs' perspective -- Petitioners' perspective in both? I mean, don't -- you have to have a theory that works, and is this not part of the theory?

MS. O'DELL: Yes, sir, no question.

THE COURT: Okay.

MS. O'DELL: It's both. But to have it dismissed

and somehow undermine the ways that we can show a logical cause and effect of a theory, in other words, that Vanessia was vaccinated on these dates and then what you see clinically manifested is exactly what appears in Mellins.

THE COURT: Mm-hmm.

MS. O'DELL: And, so -- and that's evidence of the disregulation ongoing. That's evidence of pro-inflammatory cytokines being elevated, primarily interleukin-1, interleukin-6, and interleukin-18, TNF-alpha.

So, he -- in analyzing both the Petitioners' theory on Prong One and for Prong Two, we felt like in regard to Mellins that he improperly disregarded Petitioners' evidence.

THE COURT: Okay.

Sir, on Prong Two, we also point out that one of Vanessia's treating rheumatologist, pediatric rheumatologists, when Vanessia's mother resisted the flu vaccine, I'm sure you remember that reference, it's Exhibit 5.

THE COURT: Mm-hmm.

MS. O'DELL: And the physician said essentially vaccines can trigger autoimmune diseases.

THE COURT: Mm-hmm.

MS. O'DELL: There's no data. We feel like if you look at the logical cause and effect that we put forth, preponderant evidence about the cause -- logical cause and

effect, if you accept our theory, if we get through Prong One, that -- that what happened in Vanessia, you can see it in her medical records. You can see the Gardasil vaccine and now we'll get to temporal association in a moment, but when she got the vaccine and the manifestations of pro-inflammatory cytokines and ultimately her diagnosis with sJIA, that that is a logical cause and effect that we have laid out in the record, that was dismissed, but that also there is not much in her medical records about physicians offering cause.

THE COURT: Mm-hmm.

MS. O'DELL: And -- and Special Master Moran goes through that and he -- in doing so -- let me get to that place in the opinion.

Excuse me, Your Honor.

THE COURT: Mm-hmm.

MS. O'DELL: One second. It says Dr. Hoffman -- he says Hoff, but I believe it's Hoffman, does not express any agreement with Ms. Koehn's concern about Gardasil. Dr. Hoffman --

THE COURT: I'm sorry, it's 2 Fs and not a T?

MS. O'DELL: Yes, sir, that's how I read the records.

THE COURT: Okay, all right. Go ahead, I'm sorry.

MS. O'DELL: But I'm not sure that's --

THE COURT: All right.

MS. O'DELL: -- incredibly germane, but page 51, he appears to have recommended the flu vaccine essentially, and in characterizing the treating physician's comment, you know, gives --

THE COURT: Is Hoffman the same fellow that said the patient didn't want to take them, and we all know there's association? Okay, but I mean, is Moran's point not that despite that he said go ahead and, you know, we want you to get the vaccine?

MS. O'DELL: He did want her to have a flu vaccine. And I guess my point, sir, and it's Exhibit 5, page 28, that the comment is discussed the important of the flu vaccine; basically he says but all vaccines and infections can trigger autoimmune response.

And I -- I mean, there is not a lot of evidence in this record from her treating physicians. That's the only bit of evidence from her treating physicians --

THE COURT: Mm-hmm.

MS. O'DELL: -- that suggests vaccines could be a trigger for sJIA. And it's not explicit. I wish that her treating doctor had said something different, but I do believe that it was not given due consideration. And, so, that would just be a smaller point, but another point I would make about the decision.

And then last, Your Honor, and in doing that, sir, I just point out something. I know that the Court is already aware of the pertinent one, which is from Graves, I'd love to just read to the Court about why a treating physician's failure to -- excuse me, I must have it with me, failure to assess cause is not surprising. And in the Graves decision, it says, and it's quoting Doe '93 on page 21 of my copy, which I think is -- this is Graves versus, of course, Secretary of Health and Human Services, 101 Federal Claims 310, I believe at page 334, it says, "Any expectation that treating physicians will record the precise biological theories behind their belief that a patient's condition was caused by a particular trigger is discordant with reality of medical treatment. Doctors are and must be concerned with treating patients, not with articulating the precise biological theories upon which they base their diagnosis."

And that becomes important -- that comment becomes important to Your Honor when you look at page 55 of the decision and where Special Master Moran, we believe, disregarded Dr. McCabe's views on specific causation when he says essentially these -- he's qualified to discuss immunologic principles -- excuse me, Your Honor, I'm at the wrong place. Let me move back here.

Let me say it this way. In regard to Dr. Rose, he says Dr. Rose has, you know, treated 150 to 200 patients with

sJIA, and we -- I don't doubt that. Dr. Rose is a rheumatologist, but I think that the comment in Doe '93, and as it's quoted in Graves, supports a conclusion that when Dr. Rose is treating a patient, his primary purpose is to treat, you know, that particular condition.

THE COURT: Mm-hmm.

MS. O'DELL: Not to develop a causation theory. Dr. McCabe, he has opinion, he says he -- his inexperience with diagnosing disease in human beings becomes more problematic. Dr. McCabe does not have the experience of Dr. Rose, who has diagnosed and treated 150 to 200 patients with sJIA. You know, and this paragraph, and I would say the totality of the opinion, but certainly here on page 55, Special Master Moran is dismissing in large measure Dr. McCabe's opinion about specific causation because he, as an immunologist, does not diagnose sJIA. There's no question about that.

But I feel like that when you look at Dr. McCabe's qualifications as an immunologist and an expert who is on, you know, congressional committees that consider what environmental triggers do in causing, you know, for governmental committees, I should say, in causing particular diseases, I mean, he has -- his professional career has been spent in looking at cause. And, so, that's not typically what a treating physician is doing.

THE COURT: Mm-hmm.

MS. O'DELL: And, so, I just feel like in doing so -- excuse me -- and let me be specific -- in dismissing essentially Dr. McCabe's discussion about causation, specific causation, was error.

THE COURT: That's Prong Two, right?

MS. O'DELL: Yes, sir.

THE COURT: Right? Okay.

MS. O'DELL: I mean, otherwise, an immunologist could never be an expert.

THE COURT: Mm-hmm.

MS. O'DELL: And, I mean, is that really the standard? I don't believe that to be -- to be the law.

Lastly, if the Court will bear with me --

THE COURT: Oh, that's fine.

MS. O'DELL: The Prong Three, we're talking about temporal association, and there -- probably just maybe a lot to say here, but let me focus on -- specifically language where Special Master Moran states on page 48, he's talking about the testimony regarding whether two months is a medically appropriate interval.

Dr. McCabe testified that a medically appropriate -- excuse me -- an interval was within six months from the beginning course of the vaccine shots. Or seven months, excuse me. And anytime within that period, but particularly

after shot two, is a -- sort of the germane window of time for the onset of the injury. And he's -- he testified that the expected interval between vaccination and the onset of JIA is predicted by the time period that measurable changes in the immune response are known to be elicited by the vaccine. This is page 129 to 131 of the record.

In efficacy studies for Gardasil vaccine based on zero, two, and six months immunization schedule, over 99 percent of vaccine were recipients sero-convert, or in other words, the vaccine becomes effective by seven months. Therefore, it follows that the humoral and cellular immune events required to achieve anti-HPV immunity or seroconversion within seven months. He gave that testimony and then we -- he testified to the onset of her symptoms being within two months.

But yet Dr. -- excuse me, Special Master Moran says there is not testimony from either Dr. McCabe or Rose saying that two months is a medically appropriate -- or is a medically appropriate window -- excuse me, is medically appropriate. In the absence of evidence, it is difficult to find that Ms. Koehn has met her burden of proof.

THE COURT: Mm-hmm.

MS. O'DELL: Well, that's arbitrary. When you look at Dr. McCabe's testimony, he outlined the appropriate timing and Vanessia's timing. And he testified to a reasonable

degree of medical -- scientific certainty, excuse me, that it occurred within the acceptable time frame. I mean, I think that is an unfair statement to say he didn't -- there's no evidence of -- regarding timing. And, I mean, if you had to say the magic words, you know, two months is good, but every -- is -- you know, he never said two months is good; he said this is the appropriate window for which --

THE COURT: Well, several months, 180 days, whatever, and he got the 180 days from -- that was treated as relevant, is it in Chao?

MS. O'DELL: Chao does have its -- it talks about the shot schedule --

THE COURT: Mm-hmm.

MS. O'DELL: -- as being, you know, zero and two and seven, so that's, I think, the windows in Chao when they were looking.

THE COURT: Okay.

MS. O'DELL: But when you look at seroconversion, I think the articles that talk about that more are the Frazer articles in JURA.

THE COURT: Okay. The gist of it is that within 180 days you're going to get whatever the effect is going to be.

MS. O'DELL: Yes, sir.

THE COURT: Okay. Okay.

MS. O'DELL: Your Honor, when you look at the totality of evidence, we feel like that there were findings that were arbitrary and capricious that we've gone through, and that there were occasions where the burden of proof required by Special Master Moran were beyond what the law requires. And, so, on that basis, we would urge the Court to grant our motion of review.

THE COURT: All right. Thank you.

MS. O'DELL: Any questions for me?

THE COURT: Not any more than I've already bothered you with. Why don't we take a 10-minute break. Were you trying to catch a plane in the next hour and a half?

MS. O'DELL: I'm on your schedule. So --

THE COURT: Okay, let's come back in 10 minutes.

MS. O'DELL: Thank you, sir.

THE COURT: All right, thanks.

LAW CLERK: The Court is in recess.

(Whereupon, the recording concluded at 11:34 a.m.)

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In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

* *		
CHERYL KOEHN,	*	
as mother and next friend of	*	No. 11-355V
VANESSIA KOEHN,	*	Special Master Christian J. Moran
	*	
Petitioner,	*	Filed: May 30, 2013
	*	
v.	*	
	*	Entitlement, HPV vaccine (Gardasil),
SECRETARY OF HEALTH	*	systemic juvenile idiopathic arthritis
AND HUMAN SERVICES,	*	(sJIA)
	*	
Respondent.	*	
* *		

P. Leigh O'Dell, Beasley, Allen, et al., Montgomery, AL, for petitioner; Darryl R. Wishard, United States Dep't of Justice, Washington, DC, for respondent.

PUBLISHED DECISION DENYING COMPENSATION[1]

Cheryl Koehn alleges that two doses of the human papillomavirus ("HPV") vaccine given to her daughter, Vanessia, caused her to suffer from systemic juvenile idiopathic arthritis ("sJIA").[2] Ms. Koehn seeks compensation from the

[1] The E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (Dec. 17, 2002), requires that the Court post this decision on its website. Pursuant to Vaccine Rule 18(b), the parties have 14 days to file a motion proposing redaction of medical information or other information described in 42 U.S.C. § 300aa–12(d)(4). Any redactions ordered by the special master will appear in the document posted on the website.

[2] The Secretary recognized the HPV vaccine as a vaccine covered in the Vaccine Program on April 20, 2007. National Vaccine Injury Compensation

(. . . continued)

National Childhood Vaccine Injury Compensation Program. 42 U.S.C. § 300aa-10 et seq. (2012). To establish that she is entitled to compensation, Ms. Koehn must fulfill the three-pronged test set forth in Althen v. Sec'y of Health & Human Servs., 418 F.2d 1274, 1278 (Fed. Cir. 2005).

Ms. Koehn relies primarily upon the opinion of Michael McCabe, Ph.D. Dr. McCabe presents an innovative theory involving cytokines to explain how an HPV vaccine can cause sJIA. The Secretary, however, undermined the persuasive value of Dr. McCabe's hypothesis by presenting a contrary opinion from Carlos Rose, M.D., a board-certified rheumatologist. As detailed in section IV below, Dr. McCabe's theory has not been tested, has not been the subject of peer-review, is not generally accepted in the relevant medical community, and is inconsistent with epidemiological studies.

The flaws in Ms. Koehn's evidence extend from the first prong of Althen to the remaining two prongs. Ms. Koehn has not established that the onset of her sJIA occurred in a temporal interval that Dr. McCabe's theory would predict. See section V. Additionally, Ms. Koehn's case lacks a "logical sequence of events" that connects her disease to the HPV vaccination as required by the second prong of Althen. See section VI.

Consequently, Ms. Koehn has not established that she is entitled to compensation. A full discussion follows.

I. Procedural History

Ms. Koehn filed her petition on June 6, 2011, and medical records on June 14, 2011. These medical records are summarized in section II.C, below. Ms. Koehn filed a report from Dr. McCabe on August 24, 2011. Exhibit 9. Due to concerns about the adequacy of the disclosure regarding Althen prong one, Ms.

Program: Addition of Meningococcal and Human Papillomavirus (HPV) Vaccines to the Vaccine Injury Table, 72 Fed. Reg. 19937. Although many petitioners have claimed that the HPV vaccine harmed them, this may be the first instance in which a claim has reached a special master for resolution. (Other HPV vaccine cases have been resolved when petitioners acknowledged that they were not likely to prevail or when the parties reached a settlement.)

Koehn filed a supplemental report from Dr. McCabe on October 3, 2011. Exhibit 27. As discussed more extensively below, in sections II.D.1.b and c, Dr. McCabe opined that the HPV vaccine caused Vanessia's sJIA. Ms. Koehn also filed the articles on which Dr. McCabe relied.

After Ms. Koehn made these submissions, the Secretary evaluated the evidence. The Secretary recommended that compensation be denied because Ms. Koehn had not satisfied any of the three elements set forth in Althen. In addition to identifying perceived flaws in Dr. McCabe's opinion, the Secretary also relied upon an opinion presented by Dr. Rose. Resp't Rep't, filed Nov. 14, 2011. The gist of Dr. Rose's opinion is that there is not adequate evidence to support the theory that the HPV vaccine can cause sJIA. See sections II.D.2.b and c, below.

The parties did not succeed in resolving the case through a settlement. Thus, the case was set for a hearing. In advance of the hearing, the parties filed briefs and additional medical literature. Dr. McCabe and Dr. Rose testified at a hearing held on June 21, 2012. Following the hearing, the parties submitted additional articles and briefs.

Ms. Koehn's claim that the HPV vaccine caused Vanessia's sJIA is ready for adjudication. The foundational elements—the HPV vaccine and sJIA—are discussed first. The following sections review Vanessia's medical history as well as the qualifications, reports, and testimony of the experts. After a short recitation of the legal standards, this decision separately analyzes Ms. Koehn's evidence for each of the Althen prongs. Section VII provides the conclusion.

II. Background

To provide context to Vanessia's medical history and the opinions of the parties' experts on the issue of vaccine causation, found below in sections II.C and D, respectively, it is helpful first to review some preliminary information concerning the vaccine Vanessia received and the condition from which she suffers. Thus, sections II.A and B provide a brief overview of human papillomavirus, HPV vaccine, and JIA.

A. Human Papillomaviruses and Human Papillomavirus Vaccines

1. Human Papillomaviruses

There are more than 130 different types of human papillomaviruses. These viruses tend to be found in cutaneous or mucosal epithelial surfaces. Some strains of human papillomavirus are relatively benign, causing warts. Other strains, in particular HPV 16 and HPV 18, cause cervical cancer. Exhibit 16 (Margaret Stanley, Immunobiology of HPV and HPV vaccines, 109 Gynecologic Oncology S15 (2008)) at S15-16.

Because of the cells that it infects, a human papillomavirus "is practically invisible to the host who remains ignorant of the pathogen for long periods of time." A human papillomavirus does not cause cytolysis,[3] necrosis,[4] or inflammation. Without exposure to the host's immune system, "there is little or no release into the local milieu of pro-inflammatory cytokines." Id. at S16. This is part of the virus's strategy for survival.

Given enough time, "most [human papillomavirus] infections resolve." But, approximately 10-20 percent of infected individuals develop persistent infections. One reason appears to be that humans produce relatively few antibodies in response to the human papillomavirus. Id. at S17.

2. Vaccines against Human Papillomaviruses

Developing an effective vaccine against human papillomaviruses was challenging, in part, because of the need to generate a robust response from the person's immune system. Exhibit 16 (Stanley) at S17-18. Researchers eventually succeeded in creating an HPV vaccine that induces "high concentrations of neutralizing antibodies." Id. at S18. An HPV vaccine can cause the host to produce more antibodies than the human papillomavirus because, in part, the vaccine is given intramuscularly, close to the lymph nodes. This delivery system

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[3] Cytolysis is the "destruction of a cell by rupture of the cell membrane with loss of cytoplasm." Dorland's Illustrated Medical Dictionary 466 (32nd ed. 2012).

[4] Necrosis is "the sum of morphological changes indicative of cell death." Dorland's at 1235.

"circumvent[s] the immune avoidance strategies of the viral intraepithelial infectious cycle." Id.

a) HPV Vaccine Composition

Another advance in the creation of vaccines against the human papillomavirus was the reproduction of a portion of the virus known as the L1 protein. The resulting virus-like particle (VLP) stimulates the immune system to produce antibodies and the antibodies confer immunity to the particular strand of the human papillomavirus. Exhibit 17 (Margaret Stanley, HPV- immune response to infection and vaccination, 5 Infectious Agents & Cancer 19 (2010)) at 2-3. There are two different vaccines against human papillomavirus. One, known as Cervarix, contains the L1 VLP for two strands, 16 and 18. The other, known as Gardasil, contains the L1 VLP for four strands, 6, 11, 16, and 18. Id. at 3. In addition to the difference in strands, Cervarix and Gardasil contain different adjuvants.[5] Cervarix uses an adjuvant known as AS04, which is comprised of a lipid and an aluminum salt. Exhibit E (Thomas Verstraeten et al., Analysis of adverse events of potential autoimmune aetiology in a large integrated safety database of AS04 adjuvanted vaccines, 26 Vaccine 6630 (2008)) at 6631. On the other hand, Gardasil uses amorphous aluminum hydroxyphosphate sulfate to increase antibody production. Transcript ("Tr.") 154; Physician's Desk Reference at 1828 (66th ed. 2012).

b) HPV Vaccine Effectiveness

Experiments on HPV vaccines have shown that "the peak geometric mean antibody concentrations achieved are at least two [logarithmic] higher than those after natural seroconversion"[6] and for "the majority of vaccinated subjects, serum antibody levels remain at concentrations greater than those found in natural infection." Exhibit 16 at S18. One article commented that "[i]t is fairly uncommon that a vaccine will produce an immune response greater than that

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[5] An adjuvant is a stimulator of a more robust immune response. See Dorland's at 32

[6] Seroconversion is "the change of a patient's serologic test from negative to positive, indicating the development of antibodies in response to infection or immunization." Dorland's at 1698.

achieved by natural infection." Exhibit 21 (Villa et al., Immunologic responses following administration of a vaccine targeting human papillomavirus Types 6, 11, 16, and 18, 24 Vaccine 5571 (2006)) at 5581.[7]

The amount of time to generate the antibody response was discussed in several articles. For example, one article reported that "vaccination induced a marked immune response, beginning approximately 1 month after the initial dose, peaking at approximately month 7, and thereafter declining to a stable plateau for 2.5 years after the last vaccine dose." Exhibit 25 (Ian Frazer, Correlating immunity with protection for HPV infection, 11 Int'l J. Infectious Diseases S10 (2007)) at S13; see also exhibit 22 (Elmar Joura et al., HPV antibody levels and clinical efficacy following administration of a prophylactic quadrivalent HPV vaccine, 26 Vaccine 6844 (2008)) at 6849; exhibit 28 (Alfonso García-Piñeres et al., Cytokine and Chemokine Profiles following Vaccination with Human Papillomavirus Type 16 L1 Virus-Like Particles, 14 Clinical & Vaccine Immunology 984 (2007)) at 986; exhibit 29 at 331.

In addition to looking at the production of antibodies in response to an HPV vaccine, researchers have also investigated the cytokine response. E.g., exhibit 28 (García-Piñeres), exhibit 32 (Rebecca T. Emeny et al., Priming of Human Papillomavirus Type 11-Specific Humoral and Cellular Immune Responses in College-Aged Women with a Virus-Like Particle Vaccine, 76 J. Virology 7832 (2002)), exhibit 30 (Thomas G. Evans et al., A Phase 1 Study of a Recombinant Viruslike Particle Vaccine against Human Papillomavirus type 11 in Healthy Adult Volunteers, 183 J. Infectious Diseases 1485 (2001)). At the hearing, relatively little attention was paid to the García-Piñeres article, Emeny article, or the Evans article because Dr. McCabe and Dr. Rose primarily discussed an article by Pinto. See, e.g., Tr. 119-20.

[7] Other studies that also reported that the vaccine produces a stronger antibody response include exhibit 29 (Ligia A. Pinto et al., Cellular Immune Responses to Human Papillomavirus (HPV)—16 L1 in Health Volunteers Immunized with Recombinant HPV-16 L1 Virus-Like Particles, 188 J. Infectious Diseases 327 (2003)) at 336; exhibit 35 (Purnima Bhat et al., Regulation of immune responses to HPV infection and during HPV-directed immunotherapy, 239 Immunological Revs. 85 (2011)) at 87; and exhibit 18 (Luciano Mariani & Aldo Venuti, HPV vaccine: an overview of immune response, clinical protection, and new approaches for the future, 8 J. Translational Med. 105 (2010)) at 107.

Dr. McCabe bases much of his opinion on the Pinto article, which, according to Dr. McCabe, is "an important paper in vaccinology, the study of vaccines." Tr. 100. The Pinto study is "a technical tour de force." Tr. 100, 103. Therefore, due to its complexity and its significance, the Pinto article is reviewed in detail.

When this study was conducted, vaccines against human papillomavirus were being developed. Dr. Pinto and colleagues designed an experiment "to better characterize the innate and acquired immune system cytokine response elicited by L1 VLP vaccination." Exhibit 26 (Ligia A. Pinto et al., HPV-16 L1 VLP vaccine elicits a broad-spectrum of cytokine responses in whole blood, 23 Vaccine 3555 (2005)) at 3556. The vaccination referenced in the Pinto article contained one protein present in Gardasil. Tr. 100.

Twenty-four women participated in the study. Blood specimens were collected before the initial injection, known as month zero. Twenty women, then, received a 50 µg dose of vaccination without adjuvant and four women received a placebo of sterile saline solution. One month later, all women were given a second injection of the same substance (either the vaccination or a placebo). At month two, more blood was drawn. At six months, the women received a third injection. At seven months, more blood was drawn. Exhibit 26 at 3556.

The researchers determined the level of cytokines for each of the three blood samples after different types of stimulation. Exhibit 26 at 3557. This process was done "in vitro," id. at 3562, meaning in glass, like a test tube. Dorland's at 956. The blood from women who received the vaccine and women who received the placebo was evaluated in the context of four substances. In the first, the blood was not stimulated at all. The researchers refer to this as the "media." In the second, the blood was stimulated with 10 µg of the virus-like particle present in the vaccine. In the third, the blood was stimulated with 1.0 µg of the virus-like particle. In the fourth, the blood was stimulated with a control known as PHA. Exhibit 26 at 3557, § 3.1; see also Tr. 292-93. The stimulation was for "24 [hours] in the absence or presence of L1 VLP or PHA." Exhibit 26 at 3559 (caption to figure 1).

As discussed below in section IV.B.3, the researchers obtained different results depending upon whether there was any stimulation. For cells in the media—meaning no stimulation—the cytokine levels stayed relatively similar from month zero to month two to month seven. "As shown in Fig. 1D, spontaneous secretion of cytokines in the absence of any stimuli (media control)

did not show any significant increases following vaccination." Exhibit 26 at 3560. For blood that was stimulated either with 10 µg or 1.0 µg of the virus-like particle, cytokines increased. "Stimulation of cells from vaccine recipients with L1 VLP (10 µg/ml) induced significant increases in the median levels of inflammatory . . . cytokines." Id. at 3557-59. "Similar patterns of cytokine production to the ones seen in response to L1 VLP at 10 µg/ml were observed when L1 VLP was tested at 1.0 µg/ml." Id. at 3559.

c) HPV Vaccine Safety

Dr. McCabe and Dr. Rose each referenced one epidemiological study that investigated the safety of an HPV vaccine.[8] One was an article by Chun Chao. Exhibit 34 (Chao et al., Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine, 271 J. Intern. Med. 193 (2012)). The other was an article by Thomas Verstraeten. Exhibit E.

(1) Chao Article

Dr. Chao and colleagues used a database to look at the medical history of nearly 190,000 women. Their goal was to determine whether women who received a dose of a quadrivalent human papillomavirus vaccine developed autoimmune diseases within 180 days after the vaccination. Exhibit 34 at 193. The researchers selected 180 days "to accommodate lag time for clinical work" necessary for the treating doctor to arrive at the correct diagnosis. Id. at 201.

The article says that the researchers looked for cases of "juvenile rheumatoid arthritis (JRA)." Id. at 194. The article explained how the researchers looked for various diseases:

[8] Dr. Rose also reproduced a portion of the package insert (also known as the manufacturer's label). See exhibit A at 3-4. The Secretary, however, did not submit the package insert as an exhibit, did not ask any questions about the package insert during direct examination of Dr. Rose, and did not cite it in her post-hearing brief. Although Ms. Koehn asked some questions about the package insert during the cross-examination of Dr. Rose, Tr. 252-60, the package insert does not affect the outcome of this case.

> The method for case identification was designed to be highly sensitive to capture any potential cases, to address potential undercoding or miscoding in the early course of an autoimmune condition. To this end, ICD-9 diagnosis codes, abnormal laboratory results or pharmacy prescriptions possibly indicative of autoimmune conditions . . . were captured.

Id. at 194-95. Information about the specific ICD-9 codes was contained in Appendix A-C. Id. at 195. However, the copy of the Chao article that was filed as exhibit 34 did not contain the appendices. See exhibit 34.

After the scope of the case ascertainment became an issue at the hearing, see Tr. 248, Dr. Rose was permitted to file the relevant appendix and a report commenting on the ICD-9 code. As a preliminary matter, Dr. Rose explained what an ICD-9 code is:

> The ICD-9 is a complex and evolving international coding system utilized by patient care providers to identify the condition or conditions suffered by their patients. The codes have a multiplicity of uses including retrospective identification of cases for public health projects (like the one in question), utilization of resources, quality assurance and adequacy of charges for rendered services.

Exhibit I (Dr. Rose's supplemental report, dated Nov. 1, 2012) at 2.[9] Dr. Rose next stated that under the ICD-9, the relevant code is 714.3, juvenile rheumatoid arthritis. Id. The Chao researchers used this code. See exhibit H (reproduction of Appendix A-1 from the Chao article). In addition, the Chao researchers also searched for medications commonly prescribed for sJIA. Exhibit I at 3. Thus, Dr. Rose concluded that "almost certainly all cases of JRA within the study population would have been detected with the methodology utilized by the investigators." Id. at 4.

Given this understanding of what the researchers did, the results can be stated. In the category of juvenile rheumatoid arthritis, the researchers found three

[9] For more information about ICD-9 codes, see Fresco v. Sec'y of Health & Human Servs., No. 06-469V, 2013 WL 364723, at *9 n.40 (Fed. Cl. Spec. Mstr. Jan. 7, 2013).

cases arising after vaccination. Exhibit 34 at 197 (table 1, column E, line 6). Among people who were not vaccinated, the researchers estimated that there were 43 cases. Id. at 199 (table 3, third column, line 6). The incidence rate ratios ("IRR") was 0.48 with a 95% confidence interval of 0.26-0.91. Id. (table 3, columns 4-5, line 6). Dr. Rose explained that because the confidence interval was below 1.0, there was "no increase in risk of developing new onset of JRA after HPV vaccination." Exhibit I at 3. Although Dr. Chao and colleagues did not make a specific finding for juvenile rheumatoid arthritis, their overall conclusion was similar. They stated that "this observational surveillance study offers some assurance that amongst a large and likely generalizable female population, no safety signal for autoimmune conditions was found following HPV4 vaccination in routine clinical use." Id. at 202.

(2) Verstraeten Article

The Verstraeten article collects several studies about the safety of vaccines containing an adjuvant known as AS04. AS04 is the adjuvant in Cervarix, not the adjuvant used in Gardasil. Exhibit E at 6631; Tr. 240 (Dr. Rose).

Dr. Verstraeten's and colleagues' goal was "to evaluate the safety of AS04 adjuvanted vaccines with regard to rates of AEs [adverse events] of potential autoimmune aetiology." Exhibit E at 6631. To address the problem that small studies may not detect rare events, Dr. Verstraeten and colleagues collected "[a]ll completed or ongoing controlled, randomised studies of ASO4 adjuvanted HPV-16/18, HSV and HBV vaccines conducted by GSK Biologicals [GlaxoSmithKline, the manufacturer of those vaccines] or collaborators," with one exception. Id. Forty-two studies were included. Id. at 6632 (table 1). More than 36,000 people received a vaccine and more than 30,000 people served as controls. Id. In regard to the number of people, Dr. Rose stated that the Verstraeten article was "the closest that we can be to an epidemiological study" because it studied "about 60,000 individuals . . . [and] covered two years of followup." Tr. 232. Dr. McCabe did not address this article.

Using a database, Dr. Verstraeten and colleagues looked for adverse events following the vaccination using terms in the Medical Dictionary for Regulatory Activities. Exhibit E at 6631. One of the terms was "juvenile arthritis," which,

according to Dr. Rose, encompasses sJIA. Id. at 6633 (table 2); Tr. 287.[10] The authors' general conclusion was their study "did not show evidence of an overall increase in relative risks for autoimmune disorders in participants receiving vaccines containing AS04 compared with controls." Exhibit E at 6633.

B. Juvenile Idiopathic Arthritis

1. Basic Information[11]

The term "juvenile idiopathic arthritis" encompasses several different diseases. The form affecting Vanessia is known as sJIA.[12] The diagnostic criteria

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[10] Another term was "rheumatoid arthritis," an autoimmune disease that Dr. Rose stated does not encompass sJIA. Exhibit E at 6634 (table 3); Tr. 287; see also Tr. 186, 197-98. Among the vaccine recipients, there were 12 cases of rheumatoid arthritis. Among the controls, there were nine cases. Exhibit E at 6634 (table 3). The relative risk was 1.17 and the 95 percent confidence interval ranged from 0.47 to 2.86. Id. at 6635 (table 4). When asked about this article, Dr. McCabe explained that a relative risk of greater than one means that the risk is increased and a relative risk of less than one means that the risk is decreased. Tr. 188.

[11] Dr. McCabe, who is not a medical doctor, testified that he learned more about sJIA by reading articles about the disease in the course of preparing his expert report. Tr. 164; see also Tr. 65 (discussing exhibit 12), 75-80 (discussing exhibit 13). Dr. Rose, who is a pediatric rheumatologist with experience in treating sJIA, generally did not challenge the accuracy of information provided about the disease. Thus, the source of information about sJIA is the set of articles filed as exhibits as well as the testimony.

[12] Other names for this same entity include Still's disease, systemic arthritis, systemic-onset juvenile rheumatoid arthritis, and systemic-onset juvenile chronic arthritis. Exhibit C (Fabrizio De Benedetti & Rayfel Schneider, Chapter 14: Systemic Juvenile Idiopathic Arthritis, in Textbook of Pediatric Rheumatology ("Textbook") (James T. Cassidy et al. eds., 6th ed. 2011)) at 236. Exhibit G contains a photocopy of the cover of this textbook, the book's publication information, and the first page (page 236) of chapter 14. For ease, all citations to this textbook will be made to exhibit C.

include: arthritis and a quotidian fever[13] for at least two weeks, plus a rash, lymphadenopathy, enlargement of the liver or spleen, or serositis. Exhibit C at 236 (relying upon the criteria set by the International League of Associations for Rheumatology).

The disease manifests in different parts of the body. Characteristically more than one joint is affected. During active inflammation, a person often experiences muscle pain, a fever and rash. The disease also causes problems in the person's spleen and lymph nodes. Less common features include problems in the heart, liver and (more rarely) the central nervous system. Exhibit C at 238-41.

"The acute manifestations of sJIA are variable in duration and last from weeks to months." Id. at 246. While approximately 40 percent of patients nearly completely recover after one course of the disease, more than half of the people afflicted "have a persistent disease course." Id. In the United States, less than 0.5 percent of people with sJIA die from it. Id. at 247.

Treatments for sJIA include "medications to minimize joint inflammation." Id. at 244. Prednisone is recommended.[14] Other drugs that have some effectiveness include anti-tumor necrosis factor,[15] anti-interleukin 6 receptors, anti-interleukin 1, methotrexate,[16] intravenous immunoglobulin, cyclosporine-A, and thalidomide. Exhibit C at 244-46.

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[13] A quotidian fever is one that "recurs every day." Dorland's at 693. The fever in sJIA is also sometimes referred to as a "hectic fever," which also means recurring each day. Id. at 692.

[14] Prednisone is a medication against inflammation and suppresses the immune system. Dorland's at 1509.

[15] An example of a pharmaceutical that inactivates tumor necrosis factor is etanercept. Dorland's at 650. Enbrel is a trademarked name for etanercept. Id. at 612.

[16] Methotrexate is a "folic acid inhibitor" used for many conditions, including "severe rheumatoid and psoriatic arthritis." Dorland's at 1151.

Studies from Europe suggest that sJIA has an annual incidence of between 0.3 and 0.8 per 100,000 children less than 16 years of age.[17] Although the onset peaks among children 1-5 years old, adolescents and adults can also develop the disease. Males and females are affected equally. Id. at 236.

2. Causes

The term name of the disease—systemic idiopathic juvenile arthritis—provides information about what is known about the cause of the disease. According to a medical dictionary, "idiopathic" means "of unknown cause or spontaneous origin." Dorland's at 912. "Idiopathic" does not mean that there is no cause. While the cause or causes of sJIA have not been found, "there is substantial evidence of a dysregulated innate immune response with consequent increased production of inflammatory cytokines." Exhibit G at 237.[18]

Cytokines are "nonantibody proteins released by one cell population . . . on contact with specific antigen, which act as intercellular mediators, as in the generation of an immune response." Dorland's at 466. Cytokines are "the ways we tell one cell to the other what to do." Tr. 279 (Dr. Rose). Cytokines are "very ubiquitous" and the cytokine response is "almost . . . universal." Id. After a person encounters an antigen, the immune system responds with the production of cytokines within hours. Tr. 281-82 (Dr. Rose), 295, 300 (Dr. McCabe).

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[17] The incidence rate refers to the number of new cases in a population over a period of time. See Dorland's 1595.

[18] An autoinflammatory disease differs from an autoimmune disease. See Dorland's at 181 (defining autoimmune and autoinflammatory). Autoimmune diseases, about which special masters often hear testimony, are caused by autoantibodies and autoreactive T cells. However, in sJIA, autoantibodies and autoreactive T cells are not involved. Thus, sJIA is not an autoimmune disease. Exhibit 13 (Elizabeth D. Mellins et al., Pathogenesis of systemic juvenile idiopathic arthritis: some answers, more questions, 7 Nature Revs. Rheumatology 416 (2011)) at 417-18.

While rheumatologists such as Dr. Mellins, distinguish autoimmune diseases from autoinflammatory diseases, Dr. Chao and Dr. Verstraeten (two epidemiologists) did not maintain this precision. Although both articles discuss "autoimmune diseases," that phrase is broad enough to include sJIA. See section II.A.2.c.

Human beings produce a finite number of types of cytokines, with perhaps as many as 40 different cytokines being identified so far. Tr. 290; see also Tr. 172 (Dr. McCabe stating he "accept[s] to a certain extent that there is a commonality in immune effector functions"). Depending on the context, cytokines have different purposes. Some cytokines promote inflammation while other cytokines are anti-inflammatory. See Tr. 78. Dr. McCabe stated that ordinarily, pro-inflammatory cytokines can act on multiple tissues and can lead to (a) increased vascular permeability, (b) fever, and (c) increased synovial inflammation. Tr. 77-78; see also exhibit 13 (Mellins) at 418-21, reproduced as exhibit 38 (PowerPoint slides) at 5.

The specific pro-inflammatory cytokines that have been implicated in the development of sJIA include interleukin ("IL") 1, IL-6, IL-7, IL-8, IL-18, macrophage inhibitory factor, and tumor necrosis factor. Exhibit C (Textbook) at 237; Tr. 66 (Dr. McCabe), 280 (Dr. Rose). "Many features of sJIA seem to be explained by the known effects of innate proinflammatory cytokines, IL-1 and IL-6 in particular." Exhibit 13 at 418.

How any of these cytokines contribute to sJIA is unknown.[19] As one textbook stated, "[t]he role of each one of these mediators is far from being clarified." Exhibit C at 237. At the hearing, Dr. McCabe recognized that the medical community did not understand what the cytokines were doing at the cellular level. Tr. 299.

Even accepting the proposition that pro-inflammatory cytokines contribute to the course of sJIA, this observation does not identify the causes of the disease because something must initiate the increase in cytokines. Hence, one of the articles cited by Dr. McCabe asks "What are the initial triggers of sJIA?" Exhibit 13 (Mellins) at 423. As Dr. Rose explained, medical researchers are generating

[19] The production of pro-inflammatory cytokines does not always result in disease. In fact, as Dr. McCabe and Dr. Rose recognize in their expert reports, the production of pro-inflammatory cytokines is a protective response that vaccines are designed to elicit. See exhibit 9 (Dr. McCabe) at 3 and exhibit A (Dr. Rose) at 6; see also exhibit 26 (Pinto). The production of these pro-inflammatory cytokines, however, is associated with diseases, including diseases other than sJIA, such as sarcoidosis and systemic lupus erythematosus. Tr. 279.

hypotheses to explain the development of pro-inflammatory cytokines. See Tr. 217.

Dr. McCabe identified three articles in which the authors stated that infections or vaccinations could be the initial cause for sJIA. Tr. 136, 142-43,145-46. One article stated, "in juvenile idiopathic arthritis (JIA) a temporal relationship between disease onset, childhood vaccination, remissions and flares hint[s] at a possible relation of JIA disease activity and vaccinations or infections." Exhibit 15 (Arash Ronaghy et al., Vaccination leads to an aberrant FOXP3 T-cell response in non-remitting juvenile idiopathic arthritis, 70 Ann. Rheum. Dis. 2037 (2011)) at 1[20] (footnote deleted without notation). Another article asserted that "[o]ne scenario is that infectious agents that are typically encountered in childhood initiate sJIA; no single environmental trigger has been identified, although this lack of an obvious candidate could point to multiple common agents being capable of initiating sJIA." Exhibit 13 (Mellins) at 417. A third article stated "[i]n juvenile idiopathic arthritis, infections and vaccinations have been suggested as two candidate triggers." Exhibit 12 (Berent Prakken et al., Juvenile idiopathic arthritis, 377 Lancet 2138 (2011)) at 2141. This article continued, "but neither has been confirmed as a trigger because of a scarcity of proper controlled, prospective studies." Id.

In the context of discussing vaccination as a possible trigger, Prakken cited two articles that were filed into the record. Exhibit 12 (Prakken) at 2141 nn. 46, 47. In both studies, the people given the vaccine already suffered from juvenile idiopathic arthritis and the researchers were examining whether the patient's disease worsened after the vaccination. One study involved the mumps, measles, and rubella ("MMR") vaccine. In a retrospective analysis of 207 patients with juvenile idiopathic arthritis (of which 17 had systemic arthritis), the researchers found "no changes in disease activity, flare occurrence or medication use after the MMR vaccination." Exhibit 43 (Marloes W. Heijstek et al., Safety of measles, mumps and rubella vaccination in juvenile idiopathic arthritis, 66 Ann. Rheum. Dis. 1384 (2007)) at 1386. Thus, the researchers concluded that the "MMR vaccination appears to be safe in JIA." Id.

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[20] This article, as submitted, does not have the same pagination as originally published in the Annals of Rheumatic Diseases.

The other study used the meningococcal C vaccination. The total number of participants was 234, including 34 with systemic arthritis. The researchers "did not detect any worsening of disease activity within 6 months after MenC vaccination." Exhibit 47 (Evelien Zonneveld-Huijssoon et al., Safety and Efficacy of Meningococcal C Vaccination in Juvenile Idiopathic Arthritis, 56 Arthritis & Rheumatism 639 (2007)) at 644.

The parties did not submit any case reports linking the Gardasil vaccine and JIA.

C. Vanessia's Medical History before and after her sJIA Diagnosis[21]

Vanessia was born in February 1995. She was generally healthy for the first 12 years of her life. In February 2008, Vanessia saw her regular doctor, Dr. Elena R. Regala for a routine check-up. Dr. Regala noted Vanessia's history of asthma. Exhibit 3 at 11. Dr. Regala's office administered the first dose of the HPV vaccine to Vanessia on this date. Id.; exhibit 2 at 3. Vanessia received the second dose of the HPV vaccine on April 18, 2008. Exhibit 2 at 3; exhibit 3 at 8.

On approximately June 21, 2008, Vanessia developed a rash all over her body. She reported to Dr. Regala on June 24, 2008, that she had this rash for "3 days." Exhibit 3 at 8. Dr. Regala suspected an allergic reaction and prescribed Benadryl and prednisone. Id. The rash disappeared in three days. Id. at 26 (notes dated July 2, 2008).

Vanessia stopped taking the prednisone and, on June 27, 2008, she developed pain in many places including her knees, thighs, and calves. Exhibit 4 at 14.[22] Dr. Regala's impression included juvenile rheumatoid arthritis. Exhibit 3 at 27.

On June 28, 2008, Vanessia was admitted to Marian Medical Center for "high fever accompanied by severe joint pains of the knees and ankles," which

[21] The parties accept the accuracy of the medical records.

[22] Given that Dr. Regala prescribed prednisone on June 24, 2008, and Vanessia reported, on June 27, 2008, that she had stopped taking prednisone, it appears that Vanessia actually took prednisone for fewer than three days.

started on June 25, 2008. Exhibit 3 at 26. While in the hospital, various laboratory tests were done. Exhibit 3 at 12-21; exhibit 4 at 6. Dr. Frank Scott, a rheumatologist, saw Vanessia. Dr. Scott's impression was that she had "probable Still's disease (systemic onset juvenile arthritis)." Exhibit 4 at 11-12. Vanessia was prescribed prednisone. By the day on which she was discharged (July 2, 2008), she had started to feel better, no longer had a fever, and was not suffering from joint pains. However, she still had a rash. When she left the hospital, her presumptive discharge diagnosis was JIA. Exhibit 4 at 6. At discharge, Dr. Regala referred Vanessia to a pediatric rheumatologist. Exhibit 3 at 11.

On July 8, 2008, Vanessia saw Dr. Deborah McCurdy, a pediatric rheumatologist at the University of California at Los Angeles Health System. Dr. McCurdy recorded that Vanessia's vaccinations were up-to-date, including a second dose of the HPV vaccine. Dr. McCurdy also noted that Vanessia's family history included JIA. Exhibit 5 at 51. Dr. McCurdy stated that Vanessia's symptoms made "sJIA very likely." Id. at 55. Dr. McCurdy continued the prescriptions for prednisone and was waiting for the results of pending laboratory studies to add methotrexate and Enbrel. Id. Dr. McCurdy sent a letter summarizing her findings to Dr. Regala on July 8, 2008. Exhibit 5 at 20-26. Dr. McCurdy's letter mentioned that Vanessia had "just received the second of three HPV vaccines." Id. at 21.

Vanessia saw Dr. Regala again on August 19, 2008. Exhibit 3 at 6. Dr. Regala knew that Vanessia was suffering from JIA from the previous correspondence with Dr. McCurdy. See exhibit 5 at 20, 24 (Dr. McCurdy's letter to Dr. Regala dated July 8, 2008). Dr. Regala administered the third dose of the HPV vaccine to Vanessia on August 19, 2008. Exhibit 3 at 6; see also exhibit 2 at 3.

On August 27, 2008, a physical therapist associated with a local public health department, Sylvia Medinger, saw Vanessia in response to a referral from Dr. McCurdy. In her history, Ms. Medinger recorded that Vanessia's dose of prednisone had ended on August 18, 2008. Vanessia was still receiving Enbrel. On August 25, 2008, Vanessia had a "flare-up . . . with fever, rash and increase in pain." Ms. Medinger evaluated Vanessia and recommended that she have physical therapy twice a week. Exhibit 8 at 48-50.

Vanessia returned to Dr. McCurdy on September 3, 2008. Vanessia recounted that she was having some symptoms after stopping prednisone. Dr. McCurdy recorded that Vanessia had "some improvement with Enbrel." Vanessia

was also taking methotrexate. Dr. McCurdy examined Vanessia and found that she had swollen knees and ankles. Dr. McCurdy's impression was that she was "improved but still [had evidence of] active [disease]" and was "better." Exhibit 5 at 45-46.

Dr. McCurdy continued to care for Vanessia and follow-up appointments were held in December 2008, 2009 (two appointments), and 2010. At these visits, Vanessia, despite her JIA, was generally "doing well." The doctors recommended that she receive the influenza vaccine and H1N1 vaccine. Exhibit 5 at 32, 41, 44, 60.

Another follow-up appointment occurred on January 12, 2011, at UCLA. This time, Vanessia saw Dr. Alice Hoftman, another pediatric rheumatologist. Dr. Hoftman's record states that Vanessia was "currently pursuing lawsuit against Gardasil. [Received] Gardasil #2, 4/08. [Diagnosed] 7/08." Exhibit 5 at 27. During this visit, Dr. Hoftman apparently recommended that Vanessia receive the flu vaccine. Despite having previously accepted the doctor recommendation that Vanessia receive a flu vaccine in 2008-2010, Ms. Koehn refused at this visit. See exhibit 5 at 28, 32 (H1N1 vaccine), 44, 60. Regarding her refusal, Dr. Hoftman wrote: "[patient's] mother refused flu vaccine this year. Discussed [with] mom the importance of this vaccine. Mom hesitant [because] Gardasil. [Discussed with] mom – no data but all vaccines and infections can trigger autoimmune response." Id. at 28.

D. Experts' Qualifications, Reports and Testimony

1. Petitioner's Expert, Michael J. McCabe, Ph.D.

a) Qualifications

Dr. McCabe earned a Ph.D. in microbiology and immunology from Albany Medical College in 1991. He worked at the Karolinska Institute in Stockholm, Sweden as a postdoctoral research associate from 1990 to 1992. In 1992, he joined the faculty of Wayne State University as a research assistant professor at the Institute of Chemical Toxicology. His research explored how chemicals, metals and other contaminants from the environment affect the immune response. He also held various other positions at Wayne State University until 2000. Exhibit 10 (curriculum vitae); Tr. 12-14, 50-53.

From 2000 to 2009, Dr. McCabe worked, first as an assistant professor and then as an associate professor, in the Department of Environmental Medicine at the University of Rochester School of Medicine and Dentistry. Dr. McCabe's duties included research, a small amount of teaching, and administration. While supervising approximately 25 scientists "working on lab-based and epidemiological research projects," Dr. McCabe's research focused on "mechanistic metal toxicology and immunotoxicology." Exhibit 10; see also Tr. 15-17, 35-37 (detailing teaching responsibilities).

In 2009, Dr. McCabe started working at Robson Forensic, Inc. as an associate. In that capacity, Dr. McCabe provides "reports and testimony toward the resolution of . . . personal injury litigation of toxicology and human health assessments involving environmental and occupational exposures to agents such as metals." Exhibit 10; see also Tr. 33-34.

Dr. McCabe has written about 40 articles that appear in peer-reviewed publications and about 12 book chapters. Most, but not all, of Dr. McCabe's publications relate to the toxicity of metals. Tr. 15, 37-39.

Dr. McCabe has contributed to select committees exploring causation. For example, Dr. McCabe participated on a National Academy of Science committee exploring beryllium alloy exposure. He reviewed proposals about Gulf War injuries for the Department of Defense. He was a co-author of a white paper about the role of the environment in developing autoimmune diseases for the National Institute of Environmental Health Sciences. Exhibit 10; Tr. 22-29.

In response to questions asked by the Secretary's counsel during voir dire, Dr. McCabe stated that he is not a medical doctor and does not treat patients. Tr. 33. He has not researched sJIA. Tr. 41. However, Dr. McCabe has been involved in a small pilot study, examining how "lead-intoxicated girls" responded to Gardasil. Tr. 42.

His current position at Robson Forensics, Inc. requires him to "review legal cases, produce reports, and testify as needed." Tr. 33. Dr. McCabe estimated that activities related to litigation provide more than 95 percent of his income with most of his work for plaintiffs. Tr. 33-34.

Ms. Koehn offered Dr. McCabe as an expert in the field of immunology to which the Secretary did not interpose an objection. Tr. 31, 50. Dr. McCabe was recognized as an expert in immunology. Tr. 53.

b) Report[23]

Dr. McCabe's report begins with a review of Vanessia's medical history. Dr. McCabe's recitation is consistent with the information presented above.

Dr. McCabe describes "juvenile rheumatoid arthritis."[24] He emphasizes that this disease is an autoinflammatory process "driven by dysregulation of the innate immune system as evidenced by a role for pro-inflammatory cytokines (e.g. IL-6, IL-1 and TNF-α)." Exhibit 27 at 2. He states, "[m]uch as the same with most human autoimmune diseases, the cause of Juvenile Rheumatoid Arthritis is thought to be multifactorial – with genetic susceptibility factors and environmental triggers working together in complex ways to initiate and perpetuate adaptive and innate immune activities resulting in tissue damage." Id. at 2-3. "[T]he basis for the argument for a causative role for these environmental triggers [referring to infections and vaccinations] comes from mechanistic considerations." Id. at 3.

Dr. McCabe also describes the HPV vaccine. Citing an article by Pinto, Dr. McCabe asserts that "[i]n individuals immunized with [HPV vaccines], high levels of both adaptive and innate immune cytokines are produced." Id. at 3. "Notably, many of these same vaccine-elicited cytokines are the pro-inflammatory cytokines that have been implicated in the etiology of JRA." Id. As made clear during the hearing, this is the essence of Dr. McCabe's theory: an HPV vaccine elicits a certain cytokine pattern (particularly IL-6) and these cytokines cause sJIA. Tr. 123.

Dr. McCabe's report also elaborates on the topic of the temporal interval that is medically appropriate for causation. Dr. McCabe cites studies that showed that within seven months of Gardasil vaccination, more than 99 percent of people have seroconverted. Exhibit 27 at 4-6. This discussion implies that it was appropriate to infer that development of a disease within seven months of a vaccination was caused by the vaccination.

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[23] Dr. McCabe's supplemental report encompasses his original report. Therefore, citations will be only to the report dated October 1, 2011 (Exhibit 27).

[24] Dr. Rose pointed out that "juvenile rheumatoid arthritis" is not the currently preferred term. Exhibit A at 4-5.

c) Testimony[25]

After presenting his qualifications, Dr. McCabe discussed Gardasil. Tr. 54-55. He summarized Vanessia's medical history, Tr. 55-61, and his synopsis is in accord with the findings of fact set forth above. Dr. McCabe premised his opinion on Vanessia's diagnosis of sJIA. Tr. 60.[26]

Dr. McCabe's next topic was explaining how Gardasil can cause sJIA. Dr. McCabe began by explaining a prevailing theory of how sJIA originates. As mentioned above in section II.B., sJIA is mediated by pro-inflammatory cytokines, such as TNF, interleukin 1, interleukin 6, and interleukin 18. The role of these pro-inflammatory cytokines leads to a classification of sJIA as an autoinflammatory disease. Tr. 65-66. According to Dr. McCabe, when a person with a genetic susceptibility encounters an environmental trigger, the person's innate immune system falls out of balance. The result of this imbalance, for some people, is sJIA. Tr. 66-69, 92-93.

Dr. McCabe testified about the Bradford Hill criteria for causation.[27] In Dr. McCabe's view, several of these criteria supported finding that Gardasil can cause sJIA. Supporting criteria include the temporal sequence, the dose-response relationship, and biological plausibility. Tr. 97-99. Another factor, experimental evidence, was the springboard into a lengthy discussion about how human beings respond to a vaccine against some types of human papillomavirus.

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[25] This section of the decision and the section on Dr. Rose's testimony summarize pertinent portions of their testimony without necessarily discussing each page of the transcript. However, the entire transcript has been reviewed.

[26] If Dr. McCabe had disagreed with the diagnosis from Vanessia's treating doctors, his testimony about an alternative diagnosis might have been problematic because Dr. McCabe is not a medical doctor.

[27] After the hearing, Ms. Koehn filed the article in which the Bradford Hill criteria appear. Exhibit 48 (Sir Austin Bradford Hill, The Environment and Disease: Association or Causation?, 7 Proc. of the Royal Society of Medicine 295 (1965)).

Dr. McCabe spoke extensively about a 2005 article written by Dr. Pinto and colleagues. Tr. 100-04; see Exhibit 26. Dr. McCabe interpreted this study as showing that a vaccine against a particular strand of human papillomavirus caused the production of various pro-inflammatory cytokines. Tr. 103-04, 110-11.

The discussion about the 2005 Pinto article flowed into testimony about a more recent article in which Dr. Pinto appears as the senior author. Exhibit 28 (García-Piñeres). Again, the authors used a vaccine against one strand, type 16, of the human papillomavirus. This study also showed that various cytokines increased after the administration of a vaccine against human papillomavirus. Tr. 117-19.

Dr. McCabe summarized his opinion why Gardasil can cause sJIA. His opinion is based, in part, upon "the scientific and medical literature that implicates proinflammatory cytokines and inflammatory responses and innate immunity in the pathogenesis of systemic juvenile arthritis." His opinion is also based, in part, upon the "scientific and medical literature that demonstrates that HPV vaccine is a strong and potent immunogen that stimulates the production of these same proinflammatory cytokines." Tr. 123.

At this point, Dr. McCabe moved to explain why Gardasil caused Vanessia's sJIA. Dr. McCabe saw evidence that Vanessia was generating pro-inflammatory cytokines in her clinical presentation, including a fever, rash and joint pain. Tr. 123. Dr. McCabe also maintained that when Vanessia was given medications intended to reduce pro-inflammatory cytokines, such as Enbrel, methotrexate, and prednisone, her disease improved. Tr. 124-25. Dr. McCabe also suggested that Vanessia's sJIA worsened after she received the third dose of Gardasil on August 19, 2008. Dr. McCabe, however, cautioned that when Vanessia received this dose, she was on anti-inflammatory therapies. Thus, whether the third dose of Gardasil caused Vanessia's sJIA to flare was "not necessarily clear." Tr. 126.

The next topic of Dr. McCabe's direct testimony was the medically appropriate interval between vaccination and the onset of symptoms. Dr. McCabe stated that any adverse consequence of the vaccination is likely to arise in "the time period that measurable changes in the immune response are known to be elicited by the vaccine." Tr. 128. Relying upon various studies, Dr. McCabe stated, by reference, that the medically appropriate immune response range would extend to approximately seven months after the vaccination. Tr. 127-29; see also exhibit 25 at S13.

Dr. McCabe's final topic was to address a study by Chun Chao and others. Exhibit 34. Despite involving approximately 189,000 people, Dr. McCabe asserted that the size of the study was not sufficiently large to detect any increase in the number of cases involving sJIA because sJIA is a rare disease. Tr. 133-34. Therefore, Dr. McCabe agrees with Berent Prakken, the author of another article on juvenile idiopathic arthritis, who recommended that "much larger studies . . . will be needed to define the role of environmental triggers in JIA." Tr. 136 (quoting exhibit 12 at 4).

For all these reasons, Dr. McCabe concluded, to a reasonable degree of scientific certainty, that the first two doses of the Gardasil vaccine caused Vanessia to develop sJIA.[28] Tr. 136-38.

On cross-examination, Dr. McCabe acknowledged that the Prakken article states "'Infections and vaccinations have been suggested as two candidate triggers, but neither has been confirmed because of the scarcity of proper control perspective studies.'" Tr. 140 (quoting exhibit 12 at 2141). The studies that looked for a connection between vaccination and juvenile idiopathic arthritis concerned the meningococcal vaccine and the MMR vaccine. Id.

Dr. McCabe stated that clinicians and basic researchers have been investigating the causes of sJIA for a long time. But, they have not identified the cause because it is a "multifactorial disease." Tr. 143-44. In this regard, Dr. McCabe stated that there is "no epidemiology that's meaningful enough to inform us" as to whether the HPV vaccine causes sJIA. Tr. 141-42. Dr. McCabe also acknowledged that he had not located any case reports describing an association between HPV vaccine and sJIA. Id. Dr. McCabe is not aware of anyone conducting a case control study of whether HPV vaccine causes sJIA. Tr. 147.

Counsel for the Secretary probed Dr. McCabe's reliance on medical articles. For example, counsel noted the 2005 Pinto article does not mention any type of arthritis, including sJIA, does not propose any theory to connect an HPV vaccine to sJIA, and does not report that anyone who received the vaccination developed any

[28] Ms. Koehn's counsel asked Dr. McCabe if he held his opinions "to a reasonable degree of scientific certainty," and Dr. McCabe answered affirmatively. Tr. 137. Dr. McCabe could have testified if he held his opinions only to a reasonable degree of scientific probability.

symptoms. Tr. 147-48. For the last point, Dr. McCabe pointed out that because the study did not report any consequence, it is impossible to know whether any test subjects experienced any adverse events. Tr. 148-49. Government counsel and Dr. McCabe reviewed similar limitations to other articles, including the García-Piñares article. Tr. 149-50.

In regard to the Chao article, Dr. McCabe stated that the researchers considered juvenile rheumatoid arthritis. Tr. 155 (citing exhibit 34 (Chao) at 197). The abstract of this article states "No autoimmune safety signal was found in women vaccinated with HPV-4."[29] Tr. 156 (quoting exhibit 34 at 193).

In Vanessia's medical history, none of her treating doctors expressed any opinion as to whether the HPV vaccine caused her to develop sJIA. Dr. McCabe did not see any indication that Vanessia's treating doctors were concerned about giving her the third dose of Gardasil after she had developed sJIA. Tr. 156-57. Dr. McCabe recognized that it appears that shortly before the third dose of Gardasil, Vanessia had stopped taking prednisone but was improving on Enbrel. Tr. 158 (citing exhibit 5 at 45-46).

Dr. McCabe stated that hypothetically, if Vanessia had not received Gardasil and still developed sJIA, then he would not know what caused her to develop the disease. Tr. 160. His opinion that Gardasil caused Vanessia to develop sJIA is based, in part, upon the timing and also upon the immunobiology of what is known about sJIA. Tr. 161.

Dr. McCabe also answered questions the undersigned asked. Dr. McCabe stated that after Ms. Koehn's counsel first contacted him, there was a hypothesis that Gardasil caused Vanessia's sJIA. He investigated whether "there was a tenable scientific argument" by conducting a scientific undertaking. He learned about sJIA. Tr. 164. He also looked for data to support the proposition that Gardasil causes an increase in pro-inflammatory cytokines. He also drew upon his experience and background. Tr. 164-65.

Dr. McCabe testified that the limited number of cytokines does not detract from his opinion that Gardasil causes a production of pro-inflammatory cytokines and these cytokines caused Vanessia's sJIA. He stated that although a tool box

[29] Gardasil is the vaccine against four strands of the human papillomavirus.

may have many tools, it is likely that a hammer was used to pound a nail. Tr. 172-73.

Dr. McCabe recognized that some of the Bradford Hill criteria do not support a finding of causation. For example, the "strength of association" is not supportive. In addition, the criteria of "analogy" would either be not supportive or not relevant. The studies involving juvenile idiopathic arthritis and either the MMR vaccine or the meningococcal vaccine do not link the disease with the vaccine. If the MMR vaccine and/or the meningococcal vaccine were analogous to Gardasil, then those studies would counter the hypothesis that Gardasil can cause sJIA. However, Dr. McCabe suggested that the MMR vaccine and the meningococcal vaccine differed from Gardasil. See Tr. 179-83.

Additionally, Dr. McCabe agreed that Gardasil is not the only cause of sJIA. This fact is easily recognized because sJIA existed before Gardasil. Tr. 173-74, 190-91.

In regard to Vanessia's case specifically, the undersigned asked how Dr. McCabe could distinguish a case of sJIA caused by Gardasil from a case of sJIA caused by something else. Dr. McCabe's response was relatively weak. Although not phrased in these terms, he essentially stated that among all the things to which Vanessia was exposed, the only possible cause for sJIA was Gardasil. See Tr. 191-94.

After a short redirect examination, Dr. McCabe confirmed that his opinion remained unchanged. He stated that Gardasil caused Vanessia's sJIA. Tr. 195-97.

2. Respondent's Expert, Carlos Rose, M.D.

a) Qualifications

Dr. Rose graduated from Argentina's University of Buenos Aires in 1977. He passed his boards for rheumatology while still in Argentina in 1983. By 1987, Dr. Rose was living in the United States, participating in an internship in pediatrics at the Medical Center of Delaware. He had successive fellowships in pediatric rheumatology, first at the Children's Hospital of Philadelphia and then at Alfred I. duPont Institute in Delaware. He has held a board certification in pediatrics with a specialty in rheumatology since 1998. Dr. Rose estimated that there are 216 pediatric rheumatologists in the United States. Exhibit B (curriculum vitae) at 1-5; Tr. 199-200.

He has worked as a staff physician in pediatric rheumatology at the Alfred I. duPont Institute since 1991. In 1994, he became chief of the rheumatology division. He has taught pediatrics at the Jefferson Medical College of Thomas Jefferson University since 1991, and he became a full professor at that school in 2002. Exhibit B at 6-7.

He has served on international committees and lectured to audiences in foreign countries. Dr. Rose has written more than 70 peer-reviewed articles. He also has written more than 25 book chapters or monographs. Some publications relate to juvenile idiopathic arthritis, but not specifically to sJIA. Exhibit B at 13-20; Tr. 202-03.

As part of voir dire, Ms. Koehn's counsel elicited the following points about Dr. Rose's qualifications. He is not an immunologist and he has not researched the role of pro-inflammatory cytokines in causing sJIA. He has not done any research on any human papillomavirus vaccine, including Gardasil. Tr. 204.

Dr. Rose stated that he has worked for the Department of Health and Human Services in the Vaccine Program for 21 years. Over that span, Dr. Rose estimated that he has reviewed approximately 60 cases. He recommended compensation in one case. Tr. 205-07.

The Secretary offered Dr. Rose as an expert in the field of pediatric rheumatology. After Ms. Koehn did not object, he was recognized in that field. Tr. 207.

b) Reports

In Dr. Rose's first report, he begins with a summary of Vanessia's medical history. Dr. Rose agrees that she suffers from sJIA. Exhibit A at 1.

He states that sJIA is an "auto-inflammatory disease[] likely associated with dis-regulation [sic] of cytokine networks likely IL-1 and IL-6 networks rather than the adaptive immune system." For this particular form of arthritis, Dr. Rose states that he is not familiar with any infections being associated with sJIA, although some infections have been associated with "transient self-limiting arthritis." In regard to the human papillomavirus, Dr. Rose states that that organism does not produce any arthritis and "no syndrome even remotely reminiscent of sJIA is seen in association with the infection." Id. at 2.

Dr. Rose rejects the idea that HPV vaccine can cause sJIA. Relying on a study that integrated many clinical trials, Dr. Rose states there was "no statistically significant difference in the event rates between vaccine and control groups." Id. at 3, 8 (citing exhibit E (Verstraeten)). Dr. Rose also reviewed the literature that Dr. McCabe cited.

Dr. Rose's first report concludes that "more likely than not Vanessia's disease emerged as the result of chance and it was not causally related to the immunizations she received." Id. at 7. Dr. Rose's supplemental report makes a similar point: "the temporal association between vaccine and disease onset is coincidental." Exhibit F at 1.

The supplemental report presents Dr. Rose's opinion regarding Dr. McCabe's cytokine theory. Dr. Rose asserts that "[t]he cytokine response is complex and cytokines that in certain circumstances are pro-inflammatory, in others are anti-inflammatory, depending on the combination of signals, the tissue in question and even perhaps the age of the individual." He maintains that "[t]he fact that similar cytokines are found in serum of sJIA patients and in vaccine response is more a reflection of the somewhat limited and stereotypical inflammatory response repertoire in mammals than a suggestion for a link [between] vaccine [and] sJIA." Id.

c) Testimony

After Dr. Rose was accepted as an expert in pediatric rheumatology, he summarized the material that he reviewed in this case. He offered his opinion that the Gardasil vaccinations were not related to Vanessia's development of sJIA. Tr. 208.

Dr. Rose agreed that Vanessia suffers from sJIA. SJIA, as set forth above, is not an autoimmune condition. It is an autoinflammatory condition. Dr. Rose explained that the treatment for sJIA is different medications, including corticosteroids (methotrexate). The purpose of some drugs is to inhibit cytokines such as interleukin 1, interleukin 6, and TNF. The way Vanessia's doctors treated her was typical. Tr. 210-14.

Dr. Rose elaborated on cytokines and sJIA. He stated that interleukin 6 may be a cause of sJIA. Even if it is not a cause, interleukin 6 influences the course of the disease. For example, peaks in interleukin 6 preceding a rise in temperature

and a hectic fever are a defining characteristic of sJIA. Interleukin 1 has also been linked causally to arthritis. Dr. Rose stated that his experience as a clinician who has seen some (but not all) patients with sJIA improve after taking drugs that control interleukin 1 and interleukin 6 informs his belief that these cytokines play a role in the disease. Tr. 215-17.

Dr. Rose disputed the relevance of Dr. McCabe's citation to the Prakken (exhibit 12), Mellins (exhibit 13), and Rongahy (exhibit 15) articles. According to Dr. Rose, although these articles mention that infections could cause juvenile idiopathic arthritis, the articles were merely generating hypotheses that could be tested. To Dr. Rose, the articles did not report any evidence supporting Dr. McCabe's theory. See Tr. 217-18. According to Dr. Rose, pediatric rheumatologists are not discussing whether an HPV vaccine can cause sJIA. Instead, pediatric rheumatologists are discussing how safe the vaccines are for patients with sJIA. Tr. 219.

Dr. Rose testified that one way to look at the safety of vaccines is to give vaccines to people who have a disease and to see what happens. For juvenile idiopathic arthritis, there were studies involving the MMR vaccine and the meningococcal vaccine. Those studies showed that the MMR vaccine and the meningococcal vaccine did not affect people with juvenile idiopathic arthritis adversely. Tr. 221-23.

Dr. Rose is not aware of any epidemiological data connecting the HPV vaccine and sJIA. He also has not seen any case reports on this topic. Tr. 220.

Dr. Rose discussed some of the articles on which Dr. McCabe relied. For the Pinto article (exhibit 26), Dr. Rose examined whether cytokines remained elevated. Constancy in elevation was important to Dr. Rose because, as a clinician, he sees patients with a pattern of continually elevated cytokines. When Dr. Rose stops medications that inhibit the production of cytokines, the patients flare. But, when Dr. Rose looked at the data presented in the Pinto article, he did not see much difference in the amount of cytokines produced at zero months, two months, and seven months. To Dr. Rose, the Pinto data is "very suggestive that the response that this vaccine elicited in these normal people has not been sustained," and thus the vaccine-elicited cytokine response differs from the sustained pattern of "upregulation" he sees in his patients with sJIA. Tr. 223-26.

According to Dr. Rose, the García-Piñares article from 2007 (exhibit 28) in which Dr. Pinto appears as the senior author makes the same point. These

experiments showed that a vaccine can stimulate the production of cytokines when administered. But, in Dr. Rose's view, these experiments do not show how a single incidence of cytokine production can cause a disease. See Tr. 227-28.

Dr. Rose also discussed the Verstraeten (exhibit E) article, which he cited in his expert report. Exhibit A at 3, 8. Dr. Rose stated that "this is the closest that we can get to an epidemiologic study. This is a study of about 60,000 individuals." Tr. 232. Dr. Rose stated that if the vaccine were "a significant trigger[,] I would expect to see one or two cases of sJIA in the vaccinees." Id. However, Verstraeten and his colleagues found "no evidence of an overall increase in relative risks for autoimmune disorders in participants receiving vaccines containing AS04 compared with controls." Exhibit E at 6633.

In regard to Vanessia, Dr. Rose said that he did not see any evidence that her treating doctors believed that the HPV vaccination caused her sJIA. Dr. Rose said that according to the standard of practice, even after Vanessia was diagnosed as having sJIA following the second dose of Gardasil, she still should receive the third dose. Dr. Rose said that he recommends that his patients with sJIA receive the HPV vaccine. For Vanessia, although she had a rash and increased joint pain after the third dose of Gardasil, Dr. Rose stated that this flare was due to the discontinuation of corticosteroids. Dr. Rose said that this pattern of stopping the medication and worsening of the condition happened earlier. Tr. 232-34.

On cross-examination, Ms. Koehn's counsel elicited the following testimony from Dr. Rose. The Verstraeten article did not involve Gardasil and involved a vaccine that had a different adjuvant from the adjuvant in Gardasil. There was some question about whether the Verstraeten article was looking for cases of sJIA. Tr. 240-44.

Dr. Rose stated that the incidence (new cases per year) of sJIA is between 0.3 and 0.8 per 100,000 people. Tr. 244. This fact was the starting point for a discussion between counsel and Dr. Rose about how large a population sample would be needed to power an epidemiological study involving sJIA. This colloquy did not provide especially helpful testimony in that Dr. Rose said, "I really need a calculator or somebody to help me to really calculate it. . . . So maybe you need 100,000. I don't really know the answer. . . . At least you need 100,000." Tr. 245-46.

Dr. Rose stated that in the Chao article, the researchers were looking for cases of "juvenile rheumatoid arthritis." Tr. 248 (discussing exhibit 34 at 194).

Dr. Rose maintained that, although the article was published in 2011, the researchers were using an out-of-date term. Dr. Rose believed that the term "juvenile rheumatoid arthritis" would capture cases of sJIA. Tr. 248-52.

Ms. Koehn's counsel also inquired about the Gardasil package insert, which Dr. Rose had cited in his expert report. Ms. Koehn's counsel raised two issues. First, whether the phase 3 or phase 4 clinical trials would have identified cases of sJIA that followed the administration of Gardasil. Dr. Rose said that if there were any cases, then they would have been reported. Second, whether the number of subjects in the clinical trials would have detected any changes in the incidence of sJIA. Dr. Rose stated that although there were about 10,000 vaccinees and a similar number of controls, if the vaccine caused sJIA, there would be some cases reported. Tr. 252-60.

d) Post-Hearing Report

Due to questions about the scope of the Chao research that arose during the hearing, Dr. Rose was permitted to file a brief supplemental report. It explained the process of identifying diseases in women who had received Gardasil. Exhibit F.

III. Standards for Adjudication

To receive compensation under the Program, Ms. Koehn must prove either: (1) that Vanessia suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table—corresponding to a vaccine that she received, or (2) that Vanessia suffered an injury that was actually caused by Gardasil. See 42 U.S.C. §§ 300aa-13(a)(1)(A) and 11(c)(1); Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317, 1319-20 (Fed. Cir. 2006). Here, Ms. Koehn is not claiming an injury listed on the Vaccine Table. Therefore, she must prove causation-in-fact.

When a petitioner proceeds on a causation-in-fact theory, a petitioner must establish three elements. The petitioner's

> burden is to show by preponderant evidence that the vaccination brought about [the] injury by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury.

Althen, 418 F.3d at 1278.

In this passage, Althen indicates that petitioner's burden of proof is a preponderance of the evidence. Accord 42 U.S.C. § 300aa−13(a)(1). The preponderance of the evidence standard, in turn, has been interpreted to mean that a fact is more likely than not. Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

Distinguishing between "preponderant evidence" and "medical certainty" is important because a special master should not impose an evidentiary burden that is too high. Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1379-80 (Fed. Cir. 2009) (reversing judgment that petitioners were not entitled to compensation); see also Lampe v. Sec'y of Health & Human Servs., 219 F.3d 1357 (2000); Hodges v. Sec'y of Health & Human Servs., 9 F.3d 958, 961 (Fed. Cir. 1993) (disagreeing with dissenting judge's contention that the special master confused preponderance of the evidence with medical certainty). In this regard, "close calls regarding causation are resolved in favor of injured claimants." Althen, 418 F.3d at 1280.

Ms. Koehn argues she has provided preponderant evidence to meet her burden under Althen to prove Vanessia's sJIA was caused in fact by her Gardasil vaccinations. An evaluation of each prong follows.

IV. Prong One from Althen – Medical Theory

The starting point for analysis is the theory proposed by the expert that "causally connect[s] the vaccination and the injury." Althen, 418 F.2d at 1278. This element of petitioner's case is sometimes referred to as answering the "can it" question. Pafford v. Sec'y of Health & Human Servs., No. 01-165V, 2004 WL 1717359, at *4, 9 (Fed. Cl. Spec. Mstr. July 16, 2004), mot. for review denied, 64 Fed. Cl. 19 (2005), aff'd, 451 F.3d 1352 (Fed. Cir. 2006).

To explain how Gardasil harmed Vanessia, Ms. Koehn presents a theory dependent upon relatively complex medical knowledge. Special masters have been instructed in how to evaluate this type of evidence. See section IV.A below. The evidence is analyzed in section IV.B.

A. Considerations of Scientific and Medical Evidence

As Congress authorized, the judges of the Court of Federal Claims have collectively issued the Vaccine Rules. 42 U.S.C. § 300aa−12(d)(2). The Vaccine Rules, in turn, provide that the special master "must consider all relevant and reliable evidence governed by principles of fundamental fairness to both parties." Vaccine Rule 8(b)(1); see Cedillo v. Sec'y of Health & Human Servs., 617 F.3d 1328, 1339 (Fed. Cir. 2010) (stating "Vaccine Rule 8(b)(1) necessarily contemplates an inquiry into the soundness of scientific evidence to be considered by special masters").

The reliability of expert testimony is a topic on which the Federal Circuit has guided special masters. The leading case is Terran v. Sec'y of Health & Human Servs., 195 F.3d 1302 (Fed. Cir. 1999). In Terran, the special master "examined" the expert's opinion "in the light of the four guideposts enumerated in Daubert," and "conclude[d] that petitioner's theory of causation is not based on reliable scientific evidence." Terran v. Sec'y of Health & Human Servs., No. 95-451V, 1998 WL 55290, at *11 (Fed. Cl. Spec. Mstr. Jan. 23, 1998) (citing Daubert v. Merrell Dow Pharma., Inc., 509 U.S. 579 (1993)). When Ms. Terran's appeal reached the Federal Circuit, she argued that "the Special Master improperly applied the Daubert factors to the expert's testimony." The Federal Circuit rejected this argument and indicated that the special master reasonably used "Daubert's questions as a tool or framework for conducting the inquiry into the reliability of the evidence." Terran, 195 F.3d at 1316.

After Terran, decisions from judges of the Court of Federal Claims have consistently cited to the Daubert criteria as useful in assessing an opinion that a vaccine can cause an injury. See, e.g., Snyder v. Sec'y of Health & Human Servs., 88 Fed. Cl. 706, 742-45 (2009); Cedillo v. Sec'y of Health & Human Servs., 89 Fed. Cl. 158, 181-82 (2009), aff'd, 617 F.3d at 1338; Bazan v. Sec'y of Health & Human Servs., 70 Fed. Cl. 687, 699 n.12 (2006) ("A special master assuredly should apply the factors enumerated in Daubert in addressing the reliability of an expert witness's testimony regarding causation."), rev'd on other grounds, 539 F.3d 1347 (Fed. Cir. 2008); Campbell v. Sec'y of Health & Human Servs., 69 Fed. Cl. 775, 781 (2006); Piscopo v. Sec'y of Health & Human Servs., 66 Fed. Cl. 49, 54 (2005).

The reliability of the expert's theory is not presumed. A "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." Moberly, 592 F.3d at 1324 (citing Terran, 195 F.3d at 1316).

Furthermore, the reliability of an expert's theory affects the persuasiveness of the evidence. Special masters may "inquir[e] into the reliability of testimony from expert witnesses. Weighing the persuasiveness of particular evidence often requires a finder of fact to assess the reliability of testimony, including expert testimony, and we have made clear that the special masters have that responsibility in Vaccine Act cases." Moberly, 529 F.3d at 1325 (citing Terran, 195 F.3d at 1316). [30]

The mere proffer of a theory does not satisfy petitioners' burden on this prong. If the special master finds that the expert's theory is supported by only an "ipse dixit," then the special master may reject this opinion. Snyder, 88 Fed. Cl. at 745 n.66 (2009) (quoting Gen. Elec. Co. v. Joiner, 522 U.S. 136, 146 (1997)); see also Cedillo, 617 F.3d at 1339 (also quoting Joiner, 522 U.S. at 146).

To avoid presenting just an unadorned statement from an expert, petitioners typically present medical articles on which the expert relies. When the petitioner

[30] In her post-hearing brief, Ms. Koehn consistently described Dr. McCabe's theory as "biologically plausible." Pet'r Br., filed Sept. 21, 2012, at 8, 12 (citing Doe 93 v. Sec'y of Health & Human Servs., 98 Fed. Cl. 553, 566-67 (2011)). The Secretary argued that Ms. Koehn was using the wrong standard. Resp't Br., filed Nov. 19, 2012, at 5 (citing Pet'r Br. at 8). Nevertheless, Ms. Koehn continued to assert that she has advanced a "biologically plausible theory of causation." Pet'r Reply Br., filed Dec. 4, 2012, at 4 (capitalization changed without notation).

As discussed in the text, Moberly establishes that the correct standard of proof in evaluating a petitioner's theory is the preponderance of the evidence. Moberly, 592 F.3d at 1322. Although Ms. Koehn is accurate in citing Doe 93 in support of a plausibility standard, another Court of Federal Claims opinion respectfully disagreed with Doe 93. Caves v. Sec'y of Health & Human Servs., 100 Fed. Cl. 119, 144 n.18 (2011). Rather than use a plausibility standard, Caves used a preponderance of the evidence standard. Id. at 132 (stating "each of [the Althen] requirements must be proven by a preponderance of the evidence"). When the Federal Circuit reviewed Caves, it affirmed without opinion pursuant to Federal Circuit Rule 36. 463 F. Appx. 932 (Fed. Cir. 2012). The Federal Circuit's Rule 36 adjudication indicates that "a judgment or decision has been entered without an error of law." Thus, the precedential authority supports the preponderance of the evidence standard.

presents medical articles, the special master may evaluate those articles.[31] Andreu, 569 F.3d at 1379-80 ("[T]he special master can consider [medical literature or epidemiological evidence] in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury.") (citing Daubert, 509 U.S. at 593-97). The Secretary, too, may offer articles that contradict a petitioner's theory. Stone v. Sec'y of Health & Human Servs., 676 F.3d 1373, 1379-80, reh'g en banc denied, 690 F.3d 1380 (Fed. Cir. 2012), cert. denied, --- S.Ct. ---, 2013 WL 328557 (2013); Bazan, 539 F.3d at 1353 (stating "[t]he government, like any defendant, is permitted to offer evidence to demonstrate the inadequacy of the petitioner's evidence on a requisite element of the petitioner's casein-chief [sic].").

In evaluating expert testimony and scientific literature, special masters should analyze scientific literature "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." Andreu, 569 F.3d at 1380. "In other words, a finding of causation in the medical community may require a much higher level of certainty than that required by the Vaccine Act to establish a prima facie case. The special master must take these differences into account when reviewing the scientific evidence." Broekelschen v. Sec'y of Health & Human Servs., 89 Fed. Cl. 336, 343 (2009), aff'd, 618 F.3d 1339 (Fed. Cir. 2010).

When an expert's opinion is not supported, the special master may find petitioner's proof was inadequate. Althen, 418 F.3d at 1278 ("A persuasive medical theory is demonstrated by 'proof of a logical sequence of cause and effect' . . . supported by 'reputable medical or scientific explanation[,]' i.e., 'evidence in the form of scientific studies or expert medical testimony.'") (quoting Grant v. Sec'y of Health & Human Servs., 956 F.2d 1144, 1148 (Fed. Cir. 1992)); see also Shapiro v. Sec'y of Health & Human Servs., 105 Fed. Cl. 353, 360 n.5 (2012) (denying motion for review and stating "the Special Master merely required that the theories be reliable and meet the preponderance of the evidence standard. He found each of [petitioner's expert's] explanations lacking in this regard, based upon major gaps and flaws in those theories, and instead was persuaded by [respondent's expert's] contradicting testimony."), aff'd mem., 2013 WL 1896173 (Fed. Cir. 2013).

[31] The special master, however, may not require medical literature. Althen, 418 F.3d at 1280.

These standards will be used to determine whether Ms. Koehn has met her burden of proof for the first prong of Althen.

B. Evidence Related to Prong One of Althen

1. Overview

Dr. McCabe's theory includes two distinct propositions: first, the production of inflammatory cytokines can cause sJIA, and, second, Gardasil can cause inflammatory cytokines. See Pet'r Br., filed Sept. 21, 2012, at 8-12 (organizing petitioner's prong one evidence around these two points). As previously summarized, Dr. McCabe relied primarily upon articles authored by Prakken, Mellins, Ronaghy, and Pinto. Exhibits 12, 13, 15 and 26.

Dr. Rose questioned the reliability of using cytokines to link Gardasil and sJIA. The formulation that: (1) Gardasil can cause an increase in particular cytokines; (2) those cytokines can contribute to sJIA; and, therefore, (3) Gardasil can be a significant factor in causing sJIA is oversimplified. The generation of cytokines is "very ubiquitous and [is] almost a universal response." Tr. 279. Further, people produce a finite number of cytokines, with perhaps as many as 40 being identified so far. Tr. 290; see also Tr. 172 (Dr. McCabe stating he "accept[s] to a certain extent that there is a commonality in the immune effector functions"). Thus, to Dr. Rose, "similarities in cytokine patterns . . . do not mean much in terms of causality." Tr. 219.

Given this dispute between the experts, the special master's responsibility is "to assess the reliability of testimony, including expert testimony" Moberly, 592 F.3d at 1325. One accepted method for evaluating the persuasiveness of an expert's opinion is to conduct an analysis using Daubert. Id. at 1324, citing Terran 195 F.3d at 1316.

The Supreme Court listed several non-exclusive factors that trial courts may consider in evaluating an expert's opinion:

> (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and, (4) whether the theory or technique enjoys general acceptance within a relevant scientific community.

Terran, 195 F.3d at 1316 n.2 (citing Daubert, 509 U.S. at 592-95). These factors will be used here.

2. Whether a Theory or Technique can be (and has been) Tested

One way to test the theory that Gardasil can cause sJIA is to administer Gardasil to people and see how many people develop the disease. These epidemiological studies are discussed separately below.

In lieu of that type of testing, scientists (including Dr. McCabe) look to criteria listed by Sir Austin Bradford Hill. See exhibit 48; see also Tr. 97 (testimony from Dr. McCabe about the Bradford Hill criteria). Two criteria that are potentially useful here are responses to other vaccines and animal models.

a) Other Vaccines

Dr. McCabe recognized that one way of inquiring was to "study exacerbation in individuals who have already been diagnosed and have the disease." Tr. 134. Dr. McCabe also stated that considering studies with other vaccines would be "a reasonable hypothesis . . . to consider with a few caveats." Tr. 181. Exploring how vaccinations affect people with a disease can inform the assessment of whether the vaccinations cause the disease. Tr. 222; see also W.C. v. Sec'y of Health & Human Servs., No. 07-456V, 2011 WL 4537877, at *14-15 (Fed. Cl. Spec. Mstr. Feb. 22, 2011) (considering three studies about flu vaccination given to people with multiple sclerosis), mot. for review denied in relevant part and granted in non-relevant part, 100 Fed. Cl. 440 (2011), aff'd 704 F.3d 1352 (Fed. Cir. 2013).

The record contains the results of two studies involving vaccines and juvenile idiopathic arthritis. In both studies, the people given the vaccine already suffered from juvenile idiopathic arthritis and the researchers were studying whether the patient's disease worsened after the vaccination. See generally, exhibit 43 (Heijstek) and exhibit 47 (Zonneveld-Huijssoon). One study involved MMR vaccine. In a retrospective analysis of 207 patients with juvenile idiopathic arthritis (of which 17 had sJIA), the researchers found "no changes in disease activity, flare occurrence or medication use after the MMR vaccination." Thus, the

researchers concluded that the "MMR vaccination appears to be safe in JIA." Exhibit 43 (Heijstek) at 1386.[32] The other study used the meningococcal C vaccination. The total number of participants was 234, including 34 with sJIA. Exhibit 47 (Zonneveld-Huijssoon) at 641. The researchers "did not detect any worsening of disease activity within 6 months after MenC vaccination." Id. at 644.

Analogizing between how other vaccines affect patients with juvenile idiopathic arthritis and how Gardasil affects patients with sJIA, Dr. Rose stated that "these two vaccines seem to have a wonderful record of safety in patients with JIA." Tr. 222. Dr. Rose added, that all vaccines, except live viral vaccines, are recommended to those who have JIA. Id.

Dr. McCabe pointed out that Gardasil induces a stronger response from the immune system than the natural infection. Tr. 181-82. Dr. McCabe also did not know whether the MMR vaccine or the meningococcal C vaccination induced the same type of cytokines as Gardasil induces. Tr. 183. Thus, the analogy between, on the one hand, either MMR vaccine or the meningococcal vaccine, and, on the other hand, Gardasil, is not perfect.

To the extent that some differences can be overlooked, the Heijstek and Zonneveld-Huijssoon studies suggest that when researchers have explored whether vaccinations affect juvenile idiopathic arthritis, they have not found that the vaccine worsens the disease. Because they are studies, the Heijstek and Zonneveld-Huijsoon findings are entitled to more weight than speculative passages in other articles. For example, a group of researchers, including Dr. Zonneveld-Huijsoon, stated "in juvenile idiopathic arthritis (JIA) a temporal relationship between disease onset, childhood vaccination, remissions and flares, hint at a possible relation of JIA disease activity and vaccinations or infections." Exhibit 15 (Ronaghy) at 1. As the Secretary argued, this language ("hint") is "equivocal." Resp't Br. at 6.

b) Animal Models

Another way to test whether a substance causes a disease is to substitute animals for people. If the animals develop the disease, then people might, too. See

[32] Dr. Heijstek and colleagues added a caveat that the statistical power of their study was limited and recommended a prospective trial. Id.

Tr. 176 (Dr. McCabe's testimony that if he had unlimited funding to study the causes of sJIA, he would "possibly look for some changes in animal models").

Here, there are no animal models for sJIA. However, animal models do exist for a related disease, macrophage activation syndrome. Dr. McCabe and Dr. Rose agreed that macrophage activation syndrome is similar to, although not exactly the same as, sJIA. Tr. 76 (Dr. McCabe), 219 (Dr. Rose), 285 (Dr. Rose), 297-98 (Dr. McCabe); see also exhibit C (Textbook) at 241 (discussing macrophage activation syndrome within a chapter on sJIA). While Dr. Rose suggested that a worsening of symptoms after injecting MAS-afflicted mice with specific vaccines would give us clues about the effects of certain vaccines compared to others, Tr. 219, 285, there was no evidence showing that this experiment was conducted.[33]

Dr. Rose further indicated that, in his opinion, this experiment is unlikely to be conducted. Dr. Rose explained that researchers are pursuing hypotheses around sJIA that are more likely to produce advancements than the theory that Gardasil can cause sJIA. Tr. 220-22.

Overall, the evidence relating to testing does not assist Ms. Koehn. From her perspective, the most favorable interpretation is that this factor is neutral (neither supporting nor discounting) because the most on-point testing has not been done. Another interpretation is that this factor is against Ms. Koehn's theory because the testing that has been done with other vaccines and sJIA has refuted a connection between those vaccines and sJIA.

3. Whether the Theory or Technique has been Subjected to Peer Review and Publication

The theory that Gardasil can cause sJIA has not been subject to peer review or publication. Dr. McCabe's attempt to combine two ideas— (1) that pro-inflammatory cytokines can cause sJIA and (2) that Gardasil can cause pro-inflammatory cytokines—appears to be unprecedented. As the Secretary points out, until Ms. Koehn's case, there was not even one case report published in the

[33] Neither party introduced any articles discussing the extent of experiments on animals with macrophage activation syndrome.

medical journals showing even a temporal sequence in which a Gardasil vaccination preceded sJIA. Resp't Br. at 9.

The peer-reviewed article on which Dr. McCabe most heavily relied was Pinto. Dr. McCabe saw Pinto as supporting his theory because Pinto demonstrates, in some circumstances, increased levels of cytokines are present seven months after vaccination. The specific part of the Pinto experiment on which Dr. McCabe relied was when blood from a vaccinated person was stimulated with the virus-like particle. See Tr. 104-12.

Dr. Rose opined that a different part of the experiment was more meaningful. He stated that for purposes of evaluating a possible connection between HPV vaccination and sJIA, the relevant portion is the media. To Dr. Rose, this part of the experiment showed how the cells "are before and after vaccination, how the cells behave when you leave them alone." Tr. 224. When Dr. Rose analyzed the data regarding the media, he saw that "for almost no cytokine there's a spontaneous release of cytokines that is different at time zero compared to time two and time seven." Tr. 225. The researchers came to the same conclusion: "As shown in Fig. 1D, spontaneous secretion of cytokines in the absence of any stimuli (media control) did not show any significant increases following vaccination." Exhibit 26 (Pinto) at 3560. In other words, each successive administration of HPV vaccine did not produce any increase in cytokines. Cytokine levels increased only when researchers reintroduced the agent against which the vaccine was designed to protect.

Dr. Rose was less interested in the data showing the production of cytokines after the blood cells were stimulated with more of the L1 virus-like particle. He stated: "[o]f course, when you stimulate with an antigen you get more" cytokines released. Tr. 265.

Despite contrary testimony from Dr. McCabe (see Tr. 293-96, 301-03), Dr. Rose's focus on the media column is logical. The blood in the media encountered the L1 virus-like particle only in the context of the three doses of vaccination. This pattern resembles what happened to Vanessia in the sense that no medical record suggests that she was exposed to a living strand of the human papillomavirus. If Vanessia encountered the human papillomavirus after the vaccination, the Pinto article predicts that she would produce a robust immune response like the ones reported for 10 µg and 1.0 µg of the virus-like particle.

The Pinto experiment also undermined the cohesiveness of Dr. McCabe's theory, particularly in regard to timing both for onset of symptoms and duration of symptoms. To review, after human beings are exposed to an antigen, they produce cytokines immediately. Tr. 281-82 (Dr. Rose's testimony that "from stimulus to response is a question of hours"). But, in Dr. McCabe's theory, the onset of disease can occur as long as seven months after vaccination. Tr. 127-29 (citing exhibit 25 (Frazer) at S13).

Dr. McCabe explained that the delay could be due to the time needed to amplify the immune system's response. Tr. 300-01; see also Tr. 295. However, the media portion of the Pinto experiment contradicts Dr. McCabe's speculation about an amplification process. In Pinto, the cytokines increased only when the blood was restimulated. When the blood was left alone, the cytokine level stayed relatively constant. This lack of continued elevation in pro-inflammatory cytokines was inconsistent with how sJIA persists. In Dr. Rose's experience in treating people with sJIA, those patients constantly need to receive medications to prevent development of pro-inflammatory cytokines. When the medication stops, the person has a flare in her (or his) disease. Tr. 224. Dr. McCabe, who is not a medical doctor, agreed that "cytokine disregulation in sJIA isn't a transient event." Tr. 305. But, when he was asked about why sJIA is a chronic disease, Dr. McCabe did not provide a persuasive explanation. Tr. 305.

Overall, the evidence relating to peer review and publication does not assist in finding that Dr. McCabe's theory is probable. The peer-reviewed articles about epidemiology are taken up separately.

4. Whether There is a Known or Potential Rate of Error and Whether There are Standards for Controlling the Error

No evidence was introduced on this topic. An error rate for Dr. McCabe's theory cannot be calculated. Thus, this factor does not constitute affirmative or negative evidence.

5. Whether the Theory or Technique Enjoys General Acceptance within a Relevant Scientific Community[34]

Except for the portion of the Prakken article discussed above, Ms. Koehn has not presented any evidence that the relevant scientific community generally accepts the theory that Gardasil can cause sJIA. See Pet'r Reply Br. at 14-15. The Secretary has presented evidence (the opinion of Dr. Rose) that shows that the theory is not generally accepted.

Dr. Rose is the head of pediatric rheumatology at the Alfred I. DuPont Hospital for Children. Exhibit B (curriculum vitae); Tr. 200. He conducts research on juvenile rheumatoid arthritis, although not on sJIA. Tr. 202. He attends conferences held by associations of rheumatologists. Tr. 283-84. He serves as an editor for Clinical Rheumatology. Exhibit B at 9. Given this background, it seems likely that if rheumatologists were considering whether Gardasil can cause sJIA, then Dr. Rose would have heard some discussion about this theory. However, Dr. Rose testified that he did not recall hearing about this idea. Tr. 284.

Furthermore, Dr. Rose stated that the general practice among rheumatologists is to recommend vaccinations for their patients with sJIA. See Tr. 219, 222. This practice reflects a belief that the benefits from vaccination outweigh the potential harm from vaccination. Although, conceivably, at some future time, rheumatologists will generally accept the theory that Gardasil can cause sJIA, the evidence in this case is that they do not.

6. Additional Considerations

In defining how district court judges should determine whether expert opinion is admissible, the Supreme Court has emphasized that the approach should be "flexible." Kumho Tire Co., Ltd. v. Carmichael, 526 U.S. 137, 150 (1999) (citing Daubert, 509 U.S. at 594). Thus, the analysis of whether the theory that

[34] Citing Capizzano, 440 F.3d at 1325, Ms. Koehn argues that a petitioner is not required to show a particular theory has general acceptance. Pet'r Br. at 15. It is correct that special masters may not require general acceptance. However, pursuant to Terran, special masters may consider whether a particular theory has general acceptance as one factor in the overall analysis. 195 F.3d at 1316.

Gardasil can cause sJIA may consider more than just the four factors explicitly listed in Daubert. Two other factors are the origins of the theory and epidemiological studies.

a) Genesis of the Expert's Theory

One consideration is why the expert came up with the opinion. On remand from the Supreme Court, the Ninth Circuit stated:

> One very significant fact to be considered is whether the experts are proposing to testify about matters growing naturally and directly out of research they have conducted independent of the litigation, or whether they have developed their opinions expressly for purposes of testifying. That an expert testifies for money does not necessarily cast doubt on the reliability of his testimony, as few experts appear in court merely as an eleemosynary gesture. But in determining whether proposed expert testimony amounts to good science, we may not ignore the fact that a scientist's normal workplace is the lab or the field, not the courtroom or the lawyer's office.

Daubert v. Merrell Dow Pharm., Inc., 43 F.3d 1311, 1317 (9th Cir. 1995).

Here, Dr. McCabe developed his theory for the purpose of litigation. From his initial consultation, he understood that petitioner was hypothesizing that Gardasil caused Vanessia's sJIA. From that starting point, Dr. McCabe investigated whether "there was a tenable scientific argument" and produced his report accordingly. Tr. 164. This factor, although not decisive, weighs against Dr. McCabe's theory.

b) Epidemiological Studies

The Federal Circuit has endorsed consideration of epidemiological studies as one factor in the special master's analysis. See W.C. v. Sec'y of Health & Human Servs., 704 F.3d 1352, 1361 (Fed. Cir. 2013) (holding that the special master was not arbitrary in denying compensation and summarizing epidemiological studies cited by the special master); Lampe, 219 F.3d at 1365 (stating "[a]n epidemiological study may be probative medical evidence relevant to a causation determination"). The special master may not find against a petitioner solely because the petitioner did not introduce supporting epidemiology. Capizzano, 440 F.3d at 1325.

Ms. Koehn acknowledges that she has not presented any epidemiology. Pet'r Br. at 15. The Secretary, on the other hand, relies upon the results of two studies that looked for but did not find an increased incidence of disease after vaccines against human papillomavirus. Resp't Br. at 7-8 (citing exhibit 34 (Chao) and exhibit E (Verstraeten)).

Ms. Koehn's cross-examination of Dr. Rose brought out two weaknesses in this reliance on the Verstraeten article. First, as mentioned above, Gardasil is not the same as Cervarix. Tr. 240. Logically, it is possible that a component of Gardasil that is not in Cervarix could cause unintended side effects that would not be identified in studies about Cervarix. Second, the size of the Verstraeten study, despite including more than 60,000 people, is still not large enough to discover an increased risk of sJIA. This argument derives from the incidence of sJIA, which is approximately 0.3 to 0.8 per 100,000 people in the United States. Tr. 244-45; but see Tr. 133 (Dr. McCabe's testimony that the incidence of sJIA is between 2 and 20 cases per 100,000 people). Given the frequency with which new cases develop, Dr. Rose was reluctant to estimate the size of an adequately powered study, although he speculated the size might be 100,000 people. Tr. 245-46.

In addition to the Verstraeten study, the other epidemiological study was authored by Chun Chao. Ms. Koehn reasonably could not repeat the attacks used against the Verstraeten article in response to the Chao article. Unlike the population Verstraeten analyzed, the Chao study subjects received Gardasil. Compare exhibit E (Verstraeten) at 6631 with exhibit 34 (Chao) at 193 and Tr. at 132 (Dr. McCabe noting that HPV-4, referred to in the Chao study, is Gardasil). In addition, Chao looked at more than twice as many women. Compare exhibit 34 (Chao) at 193 (n = 189,629) with exhibit E (Verstraeten) at 6630 (n = 68,512). Instead, Ms. Koehn called into question the supposition that Chao researchers would have identified cases of sJIA. See Pet'r Reply Br. at 14.

Based on the population analyzed by Chao and her colleagues and the incidence of sJIA, the study appears to be robust. According to the results, however, "no cluster of disease onset in relation to vaccination timing, dose sequence or age was found for any autoimmune condition." Exhibit 34 at 193. In other words, "[n]o autoimmune safety signal was found in women vaccinated with HPV4." Id. While an epidemiological study cannot prove that Gardasil does not cause autoimmune diseases as an absolute proposition, the results suggest that Gardasil causes an autoimmune disease extremely rarely, if it causes an autoimmune disease at all.

Taken together, the Verstraeten and the Chao articles are an additional (but not decisive) reason for finding that Dr. McCabe's theory that a vaccine against human papillomavirus can cause sJIA to be unlikely. The same result would have occurred even if the epidemiological studies were not part of the record.

C. Summary

The Supreme Court has recognized that a novel theory that is relatively unexamined by the relevant scientific community may not be as persuasive as a theory that has been thoroughly peer-reviewed. This is so because "submission to the scrutiny of the scientific community . . . increases the likelihood that substantive flaws in methodology will be detected." Daubert, 509 U.S. at 593-94. The Daubert Court added, however, that the lack of publication is a "relevant, though not dispositive, consideration in assessing . . . scientific validity." Id. at 594. Special masters, too, have recognized that a theory's novelty is not dispositive in determining its scientific validity. Cedillo v. Sec'y, Health & Human Servs., No. 98-916V, 2009 WL 331968, at *111 (Fed. Cl. Spec. Mstr. Feb. 12, 2009) ("At times novel theories can be persuasive."), mot. for review denied, 89 Fed. Cl. 158, aff'd, 617 F.3d 1328. Ultimately, however, it is petitioner's burden to support her theory with "sufficient supportive evidence to justify the adoption of a proffered new theory." Cedillo, 2009 WL 331968, at *111.

With respect to the first prong of Althen, Ms. Koehn's burden is to establish that Gardasil can cause sJIA. Her proof does not need to be scientifically certain; preponderant evidence suffices.

Here, the evidence does not weigh in Ms. Koehn's favor. Dr. McCabe, a Ph.D. immunologist, has pieced together a theory that, although not entirely impossible, contains sufficient gaps to make it unpersuasive. See Joiner, 522 U.S. at 146 (affirming exclusion of an expert's report when the trial court "conclude[d] that there [was] simply too great an analytic gap between the data and the opinion proffered"). Consequently, Ms. Koehn has not met her burden of proof.

V. Prong Three from Althen – Timing[35]

Petitioners are required to establish a "showing of a proximate temporal relationship between vaccination and injury." Althen, 418 F.3d at 1278. The Federal Circuit has elaborated that the third prong of the Althen test requires "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." Bazan, 539 F.3d at 1352. "Under this test, petitioner [is] first required to establish the timeframe for which it is medically acceptable to infer causation, that is, the timeframe in which symptoms would be expected to arise if the [disease] was caused by the vaccination. Then, she [is] obliged to show that the onset of her [disease] occurred during this causation period." Shapiro v. Sec'y of Health & Human Servs., 101 Fed. Cl. 532, 542 (2011), recons. denied after remand, 105 Fed. Cl. 353 (2012), aff'd mem., 2013 WL 1896173 (Fed. Cir. 2013).

These two aspects are separately considered, beginning with findings related to when Vanessia's sJIA began. After the relevant time for Vanessia is established, the next section reviews whether her onset date falls within a medically acceptable timeframe.

A. What happened to Vanessia

Vanessia received the first dose of Gardasil on February 18, 2008, and the second dose on April 18, 2008. Exhibit 2 at 3. The experts agree that Vanessia's sJIA became manifest in late June 2008. See Tr. 129 (Dr. McCabe stating "the disease emerged manifest in June of 2008"); Exhibit A (Dr. Rose's report) at 1.[36] As the Secretary points out, the interval between vaccination and onset is approximately four months (using the date of the first dose) and approximately two months (using the date of the second dose). See Resp't Br. at 14.

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[35] Since the third prong of Althen ties directly to Dr. McCabe's theory, this decision discusses the third prong now. The second prong of Althen is discussed in section VI.

[36] Facts supporting the onset include: On June 21, 2008, Vanessia reported she had a rash all over her body. Exhibit 3 at 8. While hospitalized, Vanessia was diagnosed with systemic onset juvenile arthritis. Exhibit 4 at 11-12.

For Ms. Koehn to prevail, she must establish that two months (or four months) falls within the medically acceptable timeframe. Bazan, 539 F.3d at 1352; Shapiro, 101 Fed. Cl. at 542.

B. Time Expected by Medical Science

The Court of Federal Claims has recognized that petitioners' proof of the medically acceptable time for an injury to appear after vaccination depends upon the petitioners presenting, pursuant to Althen prong one, a "reputable theory as to how the vaccination could cause the injury." Langland v. Sec'y of Health & Human Servs., 109 Fed. Cl. 421, 443 (2013). This linkage makes sense. If medical science understands how an injury might occur, then there would be some basis for understanding when the injury would occur. Conversely, if there is little understanding about the cause of a disease, then it is difficult to say when the disease should begin.[37] See Veryzer v. Sec'y of Health & Human Servs., 100 Fed. Cl. 344, 356 (2011) ("[T]he 'etiology' of the disorder determines the appropriate temporal relationship."), aff'd without opinion, 475 Fed. Appx. 765 (Fed. Cir. 2012). Moreover, analyzing the medically appropriate time from prong three in terms of the medical theory from prong one is in accord with the observation that evidence from one prong may overlap with another prong. Capizzano, 440 F.3d at 1326.

To Dr. McCabe, the "expected interval between vaccination . . . and the onset of the autoinflammatory disease is predicted by the time period that measurable changes in the immune response are known to be elicited by the vaccine." Tr. 128. As discussed above, people receiving Gardasil produce antibodies against the human papillomavirus within seven months. See exhibit 25 (Frazer) at S13. Therefore, Dr. McCabe implies that an appropriate timeframe in which an individual can first exhibit symptoms of sJIA caused by Gardasil extends to up to seven months. See Pet'r Reply Br. at 16 ("[I]t follows that the interval

[37] Dr. Rose expressed this idea when he stated "two months is as good as two hours or as good as six months since we really don't know what's going on." Tr. 308.

during which sJIA could be said to have a temporal association with Gardasil is the same 3-dose time frame, or within 7 months.").[38]

Dr. Rose questioned why a theory involving cytokines could produce an injury after a delay of several months. As discussed in reference to Althen prong one, Dr. Rose stated, and Dr. McCabe agreed, that the immune system produces cytokines very quickly after it encounters an antigen. Tr. 281-82 (Dr. Rose); Tr. at 295 (Dr. McCabe). Thus, Dr. Rose expected that if vaccine-triggered cytokines contributed to the pathogenesis of sJIA, then symptoms of sJIA would "start[] right away." Tr. 282.

Dr. McCabe's theory holds that cytokines that are produced in response to the vaccination could lead to sJIA. He acknowledged that sJIA has genetic factors, "meaning that certain susceptible members of the population likely exist and develop this disease with or without environmental triggers." Tr. 76. He then added that cytokines, activated by the vaccine, act on multiple tissues causing fever and the release of acute phase reactive proteins. Tr. 77-80. In his PowerPoint, he also acknowledged increased vascular permeability and increased synovial inflammation in response to cytokine activation. Exhibit 38 at slide 5 (reproducing figure 1 from exhibit 13 (Mellins) at 419). When asked to explain how the vaccine-stimulated cytokines cause the disease, Dr. McCabe referred to these consequences. Tr. 299. He also expected that "cytokine-mediated interactions between cells of the adaptive immune system and the innate immune system . . . are somehow playing a role in the disease," but more sophisticated information was lacking. Tr. 299-300.

The lack of specificity in Dr. McCabe's theory creates a gap in Ms. Koehn's case. The consequences of cytokine production that Dr. McCabe identifies, such as fever, are usually apparent very quickly. The body's rapid cytokine response appears inconsistent with Dr. McCabe's assertion that the onset of disease could take many months.

Dr. McCabe attempted to answer this conundrum by opining that the onset of sJIA could be delayed because "there's an amplification process." Tr. 301. However, Dr. McCabe did not explain persuasively what he meant by that term.

[38] As discussed below, Dr. McCabe did not directly discuss the interval in Vanessia's case, which is two months.

see also Tr. 295. And specifically, Dr. McCabe did not explain why the immune system's production of cytokines would be amplified for weeks and months without a stimulant being present.

In sum, the record does not support a finding that the medically appropriate interval for a cytokine-mediated theory would extend out to seven months as Dr. McCabe proposed. Seven months might be appropriate for a different theory.[39] And seven months might be appropriate for a cytokine-mediated theory if there were some reliable evidence about how the cytokines start a lengthy process. But, because cytokines exist for a short duration, a preponderance of evidence does not support the finding that seven months is an appropriate medical interval.

More important for Ms. Koehn's case is whether a preponderance of the evidence establishes that two months is a medically appropriate interval because Vanessia's sJIA symptoms were recognized approximately two months after the second dose of Gardasil. See section V.A above. There was no testimony from either Dr. McCabe or Dr. Rose saying that two months is medically appropriate. In the absence of evidence, it is difficult to find that Ms. Koehn has met her burden of proof. Even two months is probably too long an interval for a cytokine-driven reaction. See James v. Sec'y of Health & Human Servs., No. 09-284V, 2010 WL 4205699, at *6 (Fed. Cl. Spec. Mstr. Sept. 30, 2010) (summarizing testimony of the petitioner's expert that a child's death 14 hours after vaccination was consistent with release of cytokines); Doe/11 v. Sec'y of Health & Human Servs., No. 99-212V, 2008 WL 4899356, at *28-30 (Fed. Cl. Spec. Mstr. Oct. 29, 2008) (discussing whether a cytokine storm can arise in four hours), mot. for review denied, 87 Fed. Cl. 1 (2009), aff'd, 601 F.3d 1349 (Fed. Cir. 2010).[40]

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[39] For example, in other cases, petitioners have proposed that a vaccine caused an autoimmune response involving either antibodies or T-cells. Ms. Koehn has not proposed a theory involving antibodies or T-cells because neither appears to be involved in the pathogenesis of sJIA. See Exhibit C (Textbook) at 236.

[40] These cases are consulted because (a) petitioner did not introduce any evidence about whether two months is a medically appropriate time and (b) special masters may use their "accumulated expertise" in evaluating the cases. Lampe, 219 F.3d at 1362 (quoting Hodges v. Sec'y of Health & Human Servs., 9 F.3d 958, 961 (Fed. Cir. 1993)).

Ultimately, a finding on Althen prong three is not needed. Even if Ms. Koehn had established that there was a proper temporal sequence, timing does not entitle her to compensation. Grant, 956 F.2d at 1148. She is also required to establish a persuasive medical theory. Althen, 418 F.3d at 1278. As explained above, she has not met the first element and the failure to meet this element means that she cannot be compensated. See Hibbard v. Sec'y of Health & Human Servs., 698 F.3d 1355, 1364-65 (Fed. Cir. 2012) (holding special master did not err in resolving the case pursuant to prong two when respondent conceded that petitioner met prong three).

VI. Prong Two from Althen – Logical Sequence of Cause and Effect

The remaining Althen prong is "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." 418 F.3d at 1278. Given the finding that Ms. Koehn has not established a persuasive theory to explain how Gardasil can cause sJIA, as a matter of logic, she cannot show that Gardasil did cause her sJIA. See Caves, 100 Fed. Cl. at 145. Nevertheless, the evidence particularly relevant to this factor is discussed for the sake of completeness.[41]

A. Factors to Consider in regard to Prong Two from Althen

While the first prong from Althen is sometimes shortened to "can it?," the second prong can be summarized as asking "did it?" See Pafford, 2004 WL 1717359, at *4-5, 9. Evidence relevant to this prong "tends to be evidence specific for the petitioner." Viscontini v. Sec'y of Health & Human Servs., No. 98-619V, 2011 WL 5842577, at *20 (Fed. Cl. Spec. Mstr. Oct. 21, 2011), mot. for review denied, 103 Fed. Cl. 600 (2012). This focus on the petitioner particularly reflects the separate inquiries into the question of general causation (Althen prong one) and question of specific causation (Althen prong two). Veryzer, 100 Fed. Cl. at 353.

[41] As part of her argument regarding Althen prong two, the Secretary argues that the two (or four) month delay between vaccination and onset of symptoms makes the logical sequence of events questionable. See Resp't Br. at 10. Because section V.B above discussed the timing issue, the analysis of Vanessia's chronology is not repeated here.

According to the Federal Circuit, the petitioner might present preponderant evidence on this prong by submitting evidence from treating doctors and/or evidence demonstrating challenge / rechallenge. Capizzano, 440 F.3d at 1325-26. This type of evidence focuses on the overriding issue in this case—whether Gardasil was a substantial factor in causing Vanessia's sJIA. See Shyface v. Sec'y of Health & Human Servs., 165 F.3d 1344, 1352 (Fed. Cir. 1999). Although Ms. Koehn argued that Vanessia's presentation was consistent with pro-inflammatory cytokines, see Pet'r Br. at 13-14 (citing Tr. 123-25), this showing merely establishes that Vanessia suffered from sJIA. It does not show that the pro-inflammatory cytokines resulted from Gardasil. To be entitled to compensation, Ms. Koehn must present additional evidence. See Moberly, 592 F.3d at 1323 (holding that an appropriate temporal onset and "a simplistic elimination of other potential causes of the injury" does not meet petitioner's burden) (quoting Althen, 418 F.3d at 1278).

B. Evidence Related to Prong Two from Althen

1. Statements of Treating Doctors

To demonstrate the "logical sequence of cause and effect," the Federal Circuit has identified statements of treating doctors as probative evidence. Capizzano, 440 F.3d at 1326. Their views, however, are not necessarily "sacrosanct." Snyder, 88 Fed. Cl. at 745 n.67.

Here, Ms. Koehn acknowledges that "Vanessia's treating physicians did not express any opinion as to whether Gardasil was a cause of her development of sJIA." Pet'r Br. at 14 (citing Tr. 157). Although this lack of connection from a treating doctor tends to make her claim less likely, Ms. Koehn points to a statement from one of Vanessia's rheumatologists, Dr. Hoftman.

Dr. Hoftman worked within the University of California at Los Angeles (UCLA) Health System. Exhibit 5 at 28. Vanessia had been seen at UCLA since July 2008. Exhibit 3 at 11; exhibit 5 at 51. Dr. Hoftman saw her on January 12, 2011, as part of a periodic follow up. Exhibit 5 at 28. In the context of presenting a plan until Vanessia's next appointment in three months, Dr. Hoftman wrote "Pt mother refused flu vaccine this year. Discussed [with] mom importance of this vaccine, risk < benefit. Mom hesitant b/c Gardasil. [Discussed with] mom – no

data but all vaccines and infections can trigger autoimmune response." Exhibit 5 at 28.[42]

Dr. Hoftman does not express any agreement with Ms. Koehn's concern about Gardasil. Dr. Hoftman actually appears to have recommended that Vanessia receive the flu vaccination and Vanessia would have been vaccinated against the flu at the January 12, 2011 appointment except that Ms. Koehn "refused flu vaccine this year." In other years after Vanessia was diagnosed with sJIA, doctors had recommended, and Ms. Koehn had accepted their recommendation, that Vanessia receive a flu vaccination. See exhibit 5 at 32, 44, 60.

2. Challenge / Rechallenge

The advice to receive a flu vaccination is not necessarily inconsistent with a theory that Gardasil caused Vanessia's sJIA because the flu vaccine is not the same as Gardasil. The more relevant inquiry is whether the doctors recommended an additional dose of Gardasil.

When patients encounter a putative causative agent a second time, they are considered to be facing a "rechallenge." See Capizzano, 440 F.3d at 1322 (stating "[a] rechallenge event occurs when a patient who had an adverse reaction to a vaccine suffers worsened symptoms after an additional injection of the vaccine"). The challenge-rechallenge paradigm is relevant to determining whether petitioners have demonstrated a "logical sequence of cause and effect." Capizzano, 440 F.3d at 1326.

When the vaccinee's medical history supports challenge-rechallenge, special masters have accepted this evidence as persuasive. Freeman v. Sec'y of Health & Human Servs., No. 04-1528V, 2009 WL 5103594, at *12 (Fed. Cl. Spec. Mstr. Dec. 9, 2012); Hall v. Sec'y of Health & Human Servs., No. 02-1052B, 2007 WL 312084, at *7 (Fed. Cl. Spec. Mstr. Oct. 4, 2007). On the other hand, petitioners have sometimes fallen short of demonstrating that their case truly fits the

[42] To the extent that Dr. Hoftman expressed an opinion that "all vaccines . . . can trigger [an] autoimmune response," Dr. Hoftman's statement provides a modicum of support for Ms. Koehn's prong one argument. It does not weigh very heavily in that regard because, as Dr. Hoftman states in that same sentence, there is "no data" for the proposition.

challenge-rechallenge model. Doe 70 v. Sec'y of Health & Human Servs., 95 Fed. Cl. 598, 608 (2010) (denying motion for review when the special master did not arbitrarily find that "the facts of petitioner's case did not fit the challenge-rechallenge model"), aff'd sub nom., Rickett v. Sec'y of Health & Human Servs., 468 Fed. Appx. 952 (Fed. Cir. 2011); Locane v. Sec'y of Health & Human Servs., No. 99-589V, 2011 WL 3855486, at *11 (Fed. Cl. Spec. Mstr. Feb. 17, 2011), mot. for review denied, 99 Fed. Cl. 715, 732 (2011), aff'd, 685 F.3d 1375 (Fed. Cir. 2012).

Here, the parties draw different conclusions from how Vanessia fared after her third vaccination. The relevant chronology shows:

Date	Event	Citation
7/1/08	Dr. Scott diagnoses Vanessia with probable sJIA while she was hospitalized	Exhibit 4 at 11-12.
7/2/08	Dr. Regala, Vanessia's pediatrician, refers Vanessia to UCLA / Dr. McCurdy	Exhibit 3 at 11.
7/8/08	Vanessia's first appointment with Dr. McCurdy. The history notes that Vanessia had received two doses of the HPV vaccine. Dr. McCurdy continued the prescriptions for prednisone, methotrexate, Enbrel.	Exhibit 5 at 51-55.
8/19/08	Dr. Regala administers the third dose of Gardasil	Exhibit 3 at 6; see also exhibit 3 at 3-4.
8/25/08	During physical therapy, Vanessia had rash, chills, and joint pain.	Exhibit 8 at 48-50.
9/3/08	Vanessia returns to Dr. McCurdy. Her current medication was Enbrel. By history, Vanessia had "some improvement [with] Enbrel," although she had "swollen knees [and] ankles." Also, by history, after Vanessia "stop[ped] prednisone, [her] rash returned." The doctor's plan included continuing Enbrel and starting methotrexate. The doctor also ordered laboratory tests and if there were an increase in "inflammatory markers[,] may need prednisone."	Exhibit 5 at 45-46.

Relying upon Dr. Rose's testimony, the Secretary interprets this sequence as contrary to the challenge-rechallenge paradigm. According to the Secretary, "if the

HPV vaccine caused or substantially contributed to Vanessia's sJIA, then it would seem logical that a third dose of it on August 19, 2008 would have significantly exacerbated her symptoms."[43] The Secretary argues that the third dose of Gardasil did not make Vanessia worse because the rash was associated with stopping prednisone, not with the administration of the vaccine. Resp't Br. at 12.

Dr. McCabe's response is to emphasize a medication that Vanessia was taking—Enbrel. When Vanessia received the third dose of Gardasil, she was also taking an "anti-inflammatory therapy." Tr. 126. Enbrel is a confounding factor. As Dr. McCabe explained: "If there were no changes, part of that would be I would suspect or wonder and consider whether well, the reason that there's no change is because at the same time that a stimulus is given an inhibitor is present." Tr. 126.

In this context, Dr. McCabe stated that trying to determine whether the third dose of Gardasil made Vanessia worse is "difficult to say" because there are "[t]oo many variables." Tr. 127. Any worsening could have been due to her stopping prednisone. Her continued use of Enbrel could have prevented any worsening that Gardasil would have caused absent the use of Enbrel.[44] In addition, there is the normal waxing and waning of sJIA.

The many confounding factors make reliance on Vanessia's experience after the third dose of Gardasil difficult in either respect. While it cannot be said that the Secretary has proven the absence of rechallenge, Ms. Koehn has not met her burden of proving that Vanessia's case constitutes an example of rechallenge.[45]

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[43] Dr. McCabe indicated that on an abstract level, this logic is an appropriate way to explore a cause and effect relationship. Tr. 125-26.

[44] Enbrel appears to help Vanessia cope with her disease. See exhibit 8 at 43 (noting, on February 25, 2009, that her hand hurt after she missed one dose of Enbrel).

[45] In its most recent report addressing whether vaccines cause injuries, the Institute of Medicine discussed the value of the rechallenge paradigm.

> It is possible that one or more of the 'challenges' in an individual case patient reporting is related to coincidental exposure; thus, the committee looked for other information. . . . The value for the

(. . . continued)

3. Relative Qualifications of Experts[46]

In weighing the persuasiveness of opinion testimony, special masters may consider the relative expertise of the witness. Locane v. Sec'y of Health & Human Servs., 685 F.3d at 1380 (stating "[t]he Special Master found Dr. Warner's testimony more persuasive than Dr. Bellanti's because of their different backgrounds and specialties and because the medical literature supports Dr. Warner's theory. . . . We find nothing arbitrary or capricious."); Stone, 676 F.3d at 1382 (noting "[t]he special master found the respondent's experts' testimony on that issue to be more reliable than Dr. Kinsbourne's in view of their more extensive and more recent experience").

Dr. McCabe is not a medical doctor. Tr. 33. While Dr. McCabe's lack of training and experience as a medical doctor could decrease the value of his opinion for any of the Althen prongs, see Resp't Br. at 4-5 (discussing Dr. McCabe's

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> committee of rechallenge cases is much greater for monophasic conditions (events that typically happen only once, e.g., vasculitis) than for relapsing-remitting conditions, such as multiple sclerosis or rheumatoid arthritis.

Institute of Medicine, Adverse Effects of Vaccines: Evidence and Causality (Kathleen Stratton et al., eds. 2012). Although reports from the Institute of Medicine have informed decisions of special masters, see, e.g., Terran, 1998 WL 55290, at *10-12, mot. for review denied, 41 Fed. Cl. 330, 337 (1998), aff'd 195 F.3d 1302 (Fed. Cir. 1999), the decision in Ms. Koehn's case does not depend upon the views of the Institute of Medicine.

[46] In addition to the relative qualifications of the experts, both sides suggest that the other side's expert may be biased. Neither of these arguments found their targets because both Dr. McCabe and Dr. Rose appeared to offer sincerely held opinions.

Nevertheless, Dr. McCabe derives more than 95 percent of his income from participating in litigation. Tr. 34. In Ms. Koehn's words, his "professional activities revolve in large measure around participation in litigation." Pet'r Reply Br. at 3. This concentration leaves Dr. McCabe open to a challenge that he is simply a professional witness.

credentials and background), the Secretary makes a particular argument for prong two. The Secretary contends that he "is not qualified to independently provide medical testimony and evidence on this issue."[47] Resp't Br. at 13.

Ms. Koehn replies that Dr. McCabe's opinion should be given "substantial weight." Pet'r Reply Br. at 3. Ms. Koehn notes that Dr. McCabe earned a Ph.D in microbiology and immunology. Id. While an assistant professor at Wayne State University, he researched cytokines. Tr. 21-22. When he moved to the University of Rochester School of Medicine and Dentistry, he led researchers who were exploring how vaccines "modulate the immune response." Tr. 20-21. Ms. Koehn argues that Dr. McCabe's specific training in immunology makes him "more qualified" than Dr. Rose "to discuss the effects of vaccines on cell biology." Pet'r Reply Br. at 2-3.

Dr. McCabe is qualified to discuss immunologic principles and that expertise naturally fits in the discussion of theory under prong one of Althen. However, when those principles are applied to Vanessia specifically as part of the prong-two analysis, Dr. McCabe's inexperience with diagnosing diseases in human beings becomes more problematic. Dr. McCabe does not have the experience of Dr. Rose, who has diagnosed and treated 150-200 patients with sJIA. Tr. 278. Thus, when it comes to evaluating their opinions, Dr. Rose's opinion is given more weight.

Dr. Rose's opinion is that Gardasil did not cause Vanessia's sJIA. To him, Vanessia's Gardasil vaccinations and her development of sJIA were "unrelated events." Tr. 208. This opinion is persuasive.

4. Summary

The Althen prong two analysis is necessary only if it is found (or assumed) that the petitioner met the burden regarding Althen prong one. In the present case, Ms. Koehn's evidence on prong one was not persuasive. Hence, the foregoing

[47] Despite this argument, the Secretary did not file a Daubert-type motion to exclude his testimony. Such a motion to exclude testimony is relatively rare in the Vaccine Program. Fresco, 2013 WL 364723, at *21; Garcia v. Sec'y of Health & Human Servs., No. 05-720V, 2010 WL 2507793, at *2 (Fed. Cl. Spec. Mstr. May 19, 2010).

analysis about Vanessia's case was undertaken for the sake of completeness and to ensure that the entire record was considered.

The evidence about Vanessia does not persuasively show that she developed sJIA because of Gardasil. Her treating doctors gave her the third dose of Gardasil after she had been diagnosed with sJIA and the treating doctors continued to recommend other vaccinations to her. These vaccinations did not clearly exacerbate Vanessia's sJIA as might be expected if the Gardasil vaccine were causative.

As discussed in the context of Althen prong three, a sequence in which the vaccination preceded the development of the disease does not establish causation. In some cases, the disease followed the vaccination only as a matter of coincidence. See Capizzano, 440 F.3d at 1327 (recognizing the possibility of coincidence).

Dr. Verstraeten anticipated that coincidence and causation might be confused. He wrote:

> Bearing in mind the background incidence of autoimmune disorders in adolescents and young adult population, it seems likely that, with broader use of HPV vaccines or other vaccines targeting this age group, autoimmune disorders will be reported in temporal association with vaccine administration even in the absence of a causal relationship.

Exhibit E (Verstraeten) at 6633. Vanessia's case fits this description. Ms. Koehn has accurately reported that Vanessia's sJIA started after the vaccination but she has not established the necessary "causal relationship."

VII. Conclusion

Through the testimony of Dr. McCabe, Ms. Koehn has presented some evidence on each of the Althen prongs. However, Dr. McCabe's opinions are not persuasive. Ms. Koehn has not established, under a more likely than not standard, that the two doses of Gardasil caused Vanessia to suffer sJIA.

She is not entitled to compensation. The Clerk's Office is instructed to enter judgment in accord with this decision unless a motion for review is filed.

IT IS SO ORDERED.

s/Christian J. Moran
Christian J. Moran
Special Master

IN THE UNITED STATES COURT OF FEDERAL CLAIMS

CHERYL KOEHN, AS MOTHER AND)
NEXT FRIEND OF VANESSIA)
KOEHN,)
Petitioner,)
)
v.) Docket No.: 11-355V
)
SECRETARY OF HEALTH AND)
HUMAN SERVICES,)
Respondent.)

Suite 1050
Office of Special Masters
1401 H Street, N.W.
Washington, D.C.

Thursday,
June 21, 2012

The parties met, pursuant to notice of the Court, at 9:00 a.m.

BEFORE: HONORABLE CHRISTIAN J. MORAN
Special Master

APPEARANCES:
For the Petitioner:
P. LEIGH O'DELL, Esquire
Beasley, Allen, Crow, Methvin, Portis & Miles
234 Commerce Street
P.O. Box 4160
Montgomery, Alabama 36103-4160
(334) 269-2343

APPEARANCES: (Cont'd.)

For the Respondent:

DARRYL R. WISHARD, Esquire

U.S. Department of Justice

Civil Division

1425 New York Avenue, N.W.

Washington, D.C. 20530

(202) 616-4357

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EXHIBITS

P R O C E E D I N G S

(9:00 a.m.)

THE COURT: Good morning, everyone. This is the case of Koehn v. Secretary of Health and Human Services, Docket No. 11-355V. And if we could begin by having counsel identify themselves for the record?

MS. O'DELL: Leigh O'Dell for the Petitioner, Your Honor.

MR. WISHARD: And Darryl Wishard for Respondent.

THE COURT: Sometimes at the start of the hearing I just like to place us in time. And today is June 21, so I think that meteorically today is the first day of summer. Certainly a summer heat wave has started in Washington, D.C.

And the summer brings us a host of law school student interns, so it's nice to see a full courthouse with people who are just beginning their careers in the legal realm -- I remember when I was in law school -- so eager and so happy to be part of any proceedings, so we welcome everybody, all the interns from the Department of Justice, Office of Special Masters, and we thank counsel for their willingness to have the interns sit in on today's hearing.

The scope of the hearing is primarily to

receive the expert testimony from Dr. McCabe and Dr. Rose. There does not seem to be any factual disputes between the parties. I'd ask the attorneys to refer to exhibit number and page number when they refer to the facts about Ms. Koehn's case. There doesn't seem to be much dispute about the facts, but if they need to refer to particular lab scores or lab tests or physical exams or findings by treating doctors, if they could refer to those by exhibit numbers and page numbers.

As I said, we're going to hear expert testimony from Dr. McCabe and Dr. Rose. Both have submitted their CVs and seem to have a very impressive background, so there's obviously a professional disagreement between the experts, and I expect that today's proceedings will be conducted with courtesy and respect, that people with different perspectives can reasonably agree about some differences, and that's what brings us to Court today.

As a tip to the experts, I've asked the attorneys to try to have the experts discuss any article that they find to be significant. The reason is that we want to take advantage of Dr. McCabe's and Dr. Rose's expertise. What I want to avoid happening is a situation where the attorneys in their posttrial

briefs to me argue that the most important exhibit is Article No. 50, and then I look in the transcript and no one's talked to me about No. 50.

Then what we would have is we would have the attorneys trying to tell me what Exhibit 50 means, but Exhibit 50 is really what the doctor should be telling me what it means, so we want to have the doctors tell me what the important articles mean.

There seems to be an agreement that Ms. Koehn suffers from systemic juvenile idiopathic arthritis, and I have understood from the parties' briefs and the expert reports and the exhibits that JIA is a taxonomic entity encompassing several types. I think that's the right way to phrase that.

And some of the articles talk about juvenile idiopathic arthritis or JIA, and it's hard for me to understand whether the articles are referring to JIA in the broad sense or if they're referring specifically to the subtype, the systemic juvenile idiopathic arthritis, so there may be times I need the experts to try to help me understand if the article is talking about JIA generally or the more specific subtype of SJIA.

On that note, I noticed that one of the recent exhibits, Petty, which is Exhibit 45, is the

ILAR 2001 classification that explains what systemic JIA is. There were some other articles about that same topic, but that one seemed to be particularly helpful.

I want to go over just a few ground rules for testimony for the witnesses. It's important to state your answer verbally, verbally meaning using words. Saying things like uh-huh or uh-uh doesn't work very well because you have the court reporter transcribe what you say, so there might be times when you're shaking your head and we can see you're shaking your head, but we're going to ask you to say yes just for the record so we have that audible response.

We should try to have only one person speak at a time. The attorneys know to let the witness finish their answer before starting the next question. The attorneys know this and then get excited and don't always do that, but we try to let that happen, but if the witnesses can try to let the attorneys finish their questions before they begin their answer.

I've told the attorneys that objections are permitted, especially for problems with the form of the question such as leading on direct or compound question. Those types of objections can be cured with asking a better question. The better question will

probably produce better evidence which will ultimately help us, so those types of objections are permitted.

There will be a time when I ask my questions, and attorneys are certainly free to interject objections to my questions. I don't claim to have any special proficiency in the way I form my questions, so that if I could ask a better question I will.

The one last directive to the witnesses, if you could check with our court reporter, Gabe, during the breaks. He'll be transcribing and he might need some help with spellings, especially some of the medical terminologies or geographic place names, so if you can check with him during the breaks we'll probably get a better transcript if you can give him some help with the spellings.

At the end of the hearing we'll discuss a schedule for filing posttrial briefs. We'll talk about whether there will be any, but we'll talk about the schedule at the end of the hearing.

If the attorneys are interested in ordering a transcript, the pricing rules that we have with the court reporting company are such that if you order the transcript -- I think today is the deadline -- then there's one price. If you order the transcript after

the hearing then you pay a higher price. So there's some incentive if you are interested in ordering the transcript to ordering it today.

And those were my introductory remarks. We talked about the need for opening statements during the pretrial conference. I've already read the parties' briefs -- actually I've read them several times

-- so I'm not sure we really need to have opening statements. Ms. O'Dell, do you need to make an opening statement?

MS. O'DELL: No, Your Honor.

THE COURT: Okay. Mr. Wishard?

MR. WISHARD: No, sir.

THE COURT: Okay. Very good. In that case, Ms. O'Dell, if you'd like to begin?

MS. O'DELL: Yes, please. I'd like to call to the witness stand Dr. Michael McCabe.

THE COURT: Dr. McCabe, if you could please remain standing for a moment.

THE CLERK: If you'll raise your right hand.

Whereupon,

MICHAEL J. McCABE, JR.

having been duly sworn, was called as a witness and was examined and testified as follows:

THE COURT: You may be seated.

DIRECT EXAMINATION

BY MS. O'DELL:

Q Good morning, Dr. McCabe.

A Good morning. How is the microphone?

THE COURT: Good.

THE WITNESS: Good.

THE COURT: The microphone is actually for recording purposes.

THE WITNESS: Very good.

THE COURT: I can hear you just fine.

THE WITNESS: Thank you.

BY MS. O'DELL:

Q Dr. McCabe, would you introduce yourself, please?

A Yes. My name is Dr. Michael J. McCabe, Jr.

Q Okay. And tell us just real quickly a little bit about yourself.

A I'm from New York. I identify as a New Yorker, born and raised in either New York City or upstate New York where I was raised and my formal education at Albany Medical College and at Siena College was largely in the corridor between Albany and Montreal.

I moved around a bit during my professional

career. After growing up in upstate New York and being educated in upstate New York, migrated to Stockholm, Sweden, where I did my postdoc at the Karolinska Institute. From the Karolinska Institute I came back to the United States for my first faculty position at an academic institution at Wayne State University.

About a dozen years ago I left Wayne State University and came to Rochester where I currently live and work at the University of Rochester Medical Center.

Q Okay. And just for the record, is Exhibit 40 your latest and most current CV?

A I believe it is.

Q Okay. Great. And thanks for the overview, but if you would give us maybe some specifics about your PhD training and specifically your postdoctoral training in Sweden would be helpful.

A So I have an exhibit here that outlines some of this information that I would direct your attention to. I have a PhD in Microbiology and Immunology that I received in 1991 from Albany Medical College. That educational background included didactic coursework, qualification, qualifying exams, research in immunology, virology, cell biology, molecular biology

and related disciplines, so fairly comprehensive and diverse educational background, higher education educational background and training in modern, basic biomedical research.

After leaving Albany Medical College, as I indicated earlier, I went to the Karolinska Institute in Stockholm. Karolinska Institute is a very prestigious international institute on a level of places like Harvard and Stanford and things of that nature. And I did a two-year postdoctoral training at the Karolinska Institute.

And the research that I performed there was largely centered on self-signaling, apoptosis or regulation of cell death processes, all of these with an immunology slant, but at the same time during this postdoctoral training phase is where I started integrating toxicology with an immunology background. So that's a snapshot of my educational background and training and the relevance of that to certain things that we're discussing here today.

Following my graduate study and my postdoctoral training, again as I indicated earlier I came back to the United States and began an academic career. I secured a position as an assistant professor at Wayne State University in Detroit and

started functioning as a principal investigator in an academic environment.

You know, much like the Karolinska Institute and Albany Medical College, Wayne State University and University of Rochester, these are prestigious institutes with very strong academic, scholarly environments, and these are places that I've been proud to be affiliated with and to have been trained at through the years.

As I was mentioning, I was functioning as a principal investigator, meaning that I had responsibilities to obtain grant funding for the research that I intended to do. This was really my main responsibility and function both while I was at Wayne State, as well as at the University of Rochester.

And I was successful in obtaining projects, funding from the NIH to fund my projects on immunology and the influence of environmental chemicals, metals and other environmental contaminants on the immune response with a goal of understanding how these may serve as environmental triggers for autoimmune or immune-mediated diseases.

And really the thinking there was we could use these environmental agents as probes to provoke

changes in the immune response and study it, and also the research had some environmental relevance as to how may susceptible populations who are exposed to these types of agents, how may their disease course be altered and how might these agents contribute to causing diseases.

Q And did your research result in the publication of scientific literature?

A It did, detailed on my CV, as the author or co-author of over 50 scientific articles, somewhere between 40 and 50 peer-reviewed scientific articles, as well as oftentimes invited by my colleagues or others in the field to write book chapters and reviews.

Q Do you serve on editorial boards?

A I do serve on editorial boards. I'm currently an associate editor or one of the associate editors for a journal, Toxicology and Applied Pharmacology. This is one of the two main toxicology journals. I'm also on the editorial board of Toxicological Sciences, which is the other main toxicology journal.

I'm on the editorial board of The Journal of Immunotoxicology, so that's a journal that's more focused on the types of things that I've just alluded

to or discussed in terms of understanding how environmental chemicals and drugs modify the immune system.

Q So have you served as a professor in your professional career?

A Yes, and that's part of this 20-year career -- 20-plus-year career -- in academia. At Wayne State University I was an assistant professor. When I migrated to University of Rochester I made a lateral move as an assistant professor and then advanced to the rank of associate professor.

During that time period, as I said, my responsibilities were mainly in research, but also included teaching, a little bit to medical students, a little bit to pharmacy students, but chiefly to graduate students enrolled in the toxicology program at University of Rochester. The toxicology program at University of Rochester is one of the top toxicology training programs for PhDs in the country and has enjoyed that prestige and that distinction for 25 or more years.

My responsibilities as a professor in teaching was lecture topics largely centered on basic immunology, autoimmune diseases and made immunity to toxicology students to have them be appropriately

equipped to understand the immune system. My view is that in order to understand how drugs and chemicals affect the immune system one has to have a strong basis of understanding of immunity, and that was my teaching mission in the Department of Environmental Medicine in the toxicology program.

And it's one that had evolved throughout my professional career. I had the same responsibilities or comparable responsibilities for teaching when I was at Wayne State University to graduate students in that program, as well as students in the Department of Pharmacology at Wayne State University, as well as Pharmaceutical Sciences. So not a, I guess, cumbersome teaching responsibility through most of my professional career, but nevertheless teaching responsibility, served as course director for the toxicology program for a number of years as well.

Also as far as interacting with students in PhD training, there's a lot of one-on-one interaction with students. I had students in my lab who were performing the research, a lot of that type of interaction and teaching and training, as well as serving on many student committees for their thesis research at the time, and really what all that means is that there's translational skills from those types

of duties that match some of the administrative things that I'll talk about in a minute, but also match the type of assessment that I'm performing in this case for analysis of disease causation.

Q Do you currently hold an academic position?

A I do. I currently hold an academic position as an adjunct associate professor at University of Rochester. So I left University of Rochester full-time in late 2009, and since that time I have had an annual renewal at the request of the chairman of the Department of Environmental Medicine, as well as the dean of the medical school, for me to maintain my affiliation, to maintain my interactions with students at the University, to guest lecture when I find it to be interesting or useful or when they'll have me.

I also guest lecture and have been called to guest lecture at other academic institutions, including New York University, where I've performed many of these same types of lectures or given these same types of lectures to graduate students on many of these same issues pertinent to immunology and the role of -- equipping those students to understand basic immunology so they can assess the roles of environmental chemicals and drugs on the immune system.

Q Very quickly, if you'll walk us through, Dr. McCabe, some of the administrative positions you've held both at Wayne State and then at University of Rochester.

A Sometimes administrative duties can be the scourge of a professional career. Some of them I've enjoyed. Some of them have been quite interesting to be involved in. I smile when I mention that business about being a scourge. We're segueing here from my interaction with students to administrative duties. There are really main functions that an academic scientist performs: Research, teaching and administrative scholarly activities.

I enjoy research very much. I still do. I enjoy teaching, interaction with students, and one of the things I always told students when I was interacting with them is that one of the best things about this profession is that you get to be a tinker and a thinker. I mean, you get to work with your hands in the laboratory, and you get to think about and construct hypotheses and ideas and then support them by the research that you do in the lab or that you have others do for you.

And as one advances in their career, what I've found, and I think it's true for many academic

sciences, they spend a whole lot less time tinking and more time thinking or more time in administrative duties.

So some of the administrative duties that I think are pertinent, and I put them on this slide purposefully, is while I was at University of Rochester full-time and while I was at Wayne State University, both of these institutions had superstructures in their grant support, what I'll describe to you as superstructures, grants to the department, and both of these institutions had grants that supported what are called environmental health science centers.

So in addition to my individual grants to support my own research, there were much larger grants that supported the departmental endeavors. At University of Rochester, the name of the environmental health science center was something along the lines of Environmental Modulators of Disease, so there was very much a disease focus or disease causation analysis focused to the academic environment that I was working in, and within that group I was the director of what was called the Immunomodulators and Immunopathogenesis Research Core.

So I had the appropriate credentials,

qualifications, background, research, mission to be leading a group of about seven scientists, all of whom were also independent principal investigators who were coming together under the umbrella of the overall mission of the environmental health science center to work in areas and collaborate on activities that fell under the umbrella of immunomodulators and immunopathogenesis. So in other words, how do drugs, chemicals, vaccines, infections modulate the immune response and how does that contribute to disease.

Comparably, while I was at Wayne State University they also had an environmental health science center focused on cellular and molecular toxicology, and there rather than being a program leader, director of a research core, I was a little bit younger in my academic career and I was a director of a facility core.

And that's relevant because it had a very strong immunology bent as well -- also had a very strong toxicology bent, but also had a very strong immunology bent -- and was focused on providing a physical, technical, intellectual resource to other center members, so some 50 center members, on techniques that they could apply to their research, many of those techniques immune-based involving flow

cytometry, cytokine analysis and things that are relevant to our discussion today.

Q Okay. Have you been identified as an expert outside the context of litigation for the purpose of determining disease causation?

A Yes, I have often. And I have some examples I believe on the next slide.

Q Why don't you walk through those examples?

A Yes. So this is a slide that captures some of my service and participation on research and regulatory review committees. These are selected committees from my CV that significantly drew on my immunology expertise and background. You know, generally speaking all of them are prestigious panels, panels that I'm proud to have served on, served with other immunologists, toxicologists in addressing certain issues relevant to environmental chemicals, environmental agents and their connection to immune-mediated diseases.

The first one is a panel that was put together by the National Institute of Environmental Health Sciences. That's a branch if NIH. And this was an expert panel, probably about a dozen scientists, epidemiologists as well as basic scientists, who came together sometime in late 2010

for meetings, but also followup. We live in an age where people can communicate from afar and maintain interactions, write proposals and white papers and things of that sort.

So significant time in examining the role of environmental agents in autoimmune disease. As I said, it involved epidemiologists, as well as basic scientists. My role in that was to work with probably a handful of other basic scientists analyzing animal study data, the animal studies that addressed certain environmental chemicals that induced autoimmune disease in animal models.

So it was really focused on mechanism, which suits my background, from my research background, focused on how animal studies can inform this issue of environmental triggers of autoimmune disease. And as I said, this was a panel that included epidemiologists so there was a complementary handful of scientists who were epidemiologists who were vetting the epidemiology studies on the same thing, and we were merging our findings.

The second one I have listed here is a research regulatory review committee that I've had a longstanding interaction with over a decade. This is called the Congressionally Directed Medical Research

Program. The Department of Defense runs their own research program and serves as a grant-funding agency for certain targeted illnesses, I believe started sometime in the late 1990s targeting breast cancer. The Army and Department of Defense got interested in that.

It actually has morphed or has developed into a very healthy funding program that has also targeted other diseases, one of which is Gulf War injury. And I have been asked almost on an annual basis, sometimes two or three times a year, to review proposals that are submitted to the CDMRP for funding to essentially assess the scientific merit of those proposals, oftentimes usually about a dozen proposals at each time, so it's a significant amount of work, and then come together in a study section type environment to discuss the programs, assess with colleagues the scientific merit of the proposals and then be able to make a recommendation back to the funding agency about the scientific merits so that they can determine which proposals should be supported.

This is relevant. This background in Gulf War injury is relevant because many of the maladies that are alleged for those individuals to be suffering

include neurological and immunological defects or some combination of immune-mediated neurological injury and so these are for that reason relevant for our discussion.

Q Just quickly if you'll tell us about the WHO?

A Sure. So the World Health Organization, I was contacted in late 2009, but really didn't start working until 2010 on one of their harmonization projects. So essentially the World Health Organization was performing an analysis very similar to what that first bullet item on National Institute of Environmental Health was, but more restricted to consideration of mercury as an inducer of autoimmune disease.

Mercury is an environmental chemical, and several publications have had grant support for this as well. It's an environmental chemical that induces autoimmune disease in animal models and so by virtue of that it serves the purposes that I spoke about in the beginning that environmental chemicals can be modulators of disease that we can use and then study disease process.

Part of this harmonization project was to understand the details of the mechanisms of immunity

in those animal models that may be translatable to human disease and consideration of whether mercury and exposure to mercury from amalgam, dental amalgam, methylmercury in fish and things of this nature as sources of exposure may produce human autoimmune disease.

I paused a little bit before talking about the World Health Organization because I wanted to also draw to your attention that, and I think we'll cover it in a few minutes here, but, as you know, I left the University of Rochester in 2009 to take a job at Robson Forensic to serve as a scientific consultant and perform activities much like I'm performing here today.

Throughout that time since 2009, I have maintained substantial, significant academic activities, some of which I already talked to in association with my adjunct appointment at the University of Rochester, my lecturing at New York University. I also consult on grants with investigators at Wayne State University, so I've maintained the bridges throughout my professional career.

I'd also point out here that many of these research and regulatory review committees and my

appointments and my participation on these committees have continued and in fact have increased in frequency since the time that I left the University of Rochester, so the call to serve on this NIEHS panel, the call to serve on the Department of Defense panels, as well as the World Health Organization, all have occurred after I left University of Rochester, and I have some other invitations for some things in the future.

Real quickly here, I just want to -- so I've been doing this type of expert work outside the area of litigation for many years, since around the mid '90s when I was first contacted and asked to start serving as a reviewer for NIH on various panels.

That's more on the bottom of the slide and really just is a short list of some of the panels that I've served on for NIH study sections to review NIH funded grants, performing many of the same types of activities that I described for the DOD panels to assess the scientific merit of proposals in these areas, and this includes things that fit my diverse background in terms of skeletal biology and regeneration study section, hypersensitivity, autoimmune and immune-mediated disease review panels, certainly the alcohol and toxicology study sections

when they existed and then also more targeted study sections on autoimmune diseases such as Sjogren's syndrome.

I skipped over I just want to briefly mention what I'm very proud about is having been asked to serve on a National Academy of Science committee back in 2007 here in Washington, and this was a committee on beryllium, alloy exposure. Again exemplifies that environmental agents can serve as triggers of disease.

Beryllium is a low molecular weight compound used -- It's an alloy that's used in fabrications within the airline industry and electrical industries, something that's very much of interest by the United States Air Force, who sponsored this study by the National Academy of Sciences. Beryllium is well known to cause human disease and cause berylliosis, a pulmonary inflammatory disease that looks very much like sarcoidosis.

And that was a panel that I participated in again as a basic scientist working with other clinicians, epidemiologists, risk assessors on this committee, and this work formulated or culminated in a publication, Managing Health Effects of Beryllium Exposure, and my function or my role in that was to

essentially write the pathogenesis section of that piece that dealt with understanding how beryllium can modify antigen presenting cells in select populations, so there's a genetic component to it as well, and drive T-cell proliferation as the main -- T-cell proliferation and T-cell mediated cytokine production as the main producer of the disease.

Q Okay. If you'll tell us, Dr. McCabe, what your specialty is and sort of the unique combination between toxicology and immunology.

A Well, I wear a couple hats. I wear a hat as a toxicologist, and as I think -- as I hope -- I've related to you here I have a fairly diverse background.

That doesn't mean I know everything. It doesn't mean I'm a jack of all trades, but it just means that over the course of time really starting with my graduate training I was interested in immunology and went to graduate school to receive training in cellular and molecular immunology, which I did and was successful at, but at the same time gained some interest in toxicology that built through my postdoc and certainly built through my professional career.

So in part I view myself as somebody who's

worn those two hats, but really operated also in the middle. You know, you could coin a term. Scientists are great at coining a term. So I'm an immunotoxicologist, and to me that means I'm an immunologist as well as a toxicologist, and that's what my specialty is and I perceive myself as having a specialty. I view the world as an immunologist oftentimes, most of the time.

Certainly in my research career I view the world as an immunologist, and I'm interested in how environmental triggers modulate the immune system and what can that tell us about function of the immune system from a basic science perspective and by understanding a functioning immune system how can that be translatable to human diseaseS.

Q Dr. McCabe, in your work in this case, have you used the same intellectual rigor that you utilized in your service on the WHO committee or one of the NIH committees?

A Sure. Yes.

Q Okay. And is that also true for the work you've done through Robson Forensic in other cases?

A Absolutely.

Q Well, why don't we transition just a moment here to Vanessia Koehn, the young woman at issue in

this case, and for purposes of the record just go through some of the pertinent medical facts, dates and other information.

THE COURT: Ms. O'Dell, were you going to offer Dr. McCabe?

MS. O'DELL: Yes, sir. At this point in time I'd like to offer Dr. McCabe as an expert in the context of immunology.

THE COURT: Mr. Wishard, did you want to voir dire?

MR. WISHARD: I do have some questions, sir. Yes.

THE COURT: Okay.

MR. WISHARD: You can stay. I'll sit here. That's fine.

MS. O'DELL: Okay. Thanks.

MR. WISHARD: If the Special Master doesn't mind if I just sit.

THE COURT: That's fine, as long as we can hear you and transcribe your comments.

MR. WISHARD: I'll try.

VOIR DIRE EXAMINATION

BY MR. WISHARD:

Q Dr. McCabe, I'm Darryl Wishard. I represent HHS. I do have some questions about your

qualifications. I noted that there were two CVs filed in this case. The first one is Exhibit 10, and the second one is Exhibit 40. I noted that in the first CV you just list your specialty as toxicologist, and your second CV, which is Exhibit 40, you list your specialty as toxicologist/immunologist. Was there any reason for that change in your CV other than this case?

A Yes, there was.

Q Okay. And what was the reason?

A This is my professional CV as seen by the world on the Robson Forensic website, for example, and when I first came to Robson Forensic it was really the toxicology hat that attracted them to me. Did I say that right? They were attracted by my toxicology background. So this was a new world for me to be stepping out of the academic world, and probably as you know I had done this type of expert work for Department of Justice in Vaccine Court in 2007.

Q I have some questions on that.

A So that was somehow related to this is that I had stepped out of the academic field into a consulting position, into industry and into private enterprise, and at first the cases that I was being asked to review had to do with toxicology.

During this transition period it became apparent to me and to others who were calling asking us to -- us meaning Robson and me meaning the immunologist/toxicologist there -- to review those types of cases as well, and so my immunology background became prominent. I wouldn't say more prominent than toxicology. It became an issue.

Q Very good. You're not a physician, correct?

A Correct.

Q You don't see or treat patients, correct?

A No, sir.

Q And as you stated, you're currently employed as an associate at Robson Forensics since 2009, correct?

A Correct.

Q And your duties at Robson are really, my understanding is, to review legal cases, produce reports and testify as needed, correct?

A Correct.

Q Can you give me an idea about percentage of annual work hours you do for Robson regarding litigation work?

A Yeah. You know, in the context of all the other professional duties that I've talked about, I would say something on the level of about 80 percent,

so certainly the majority.

Q Okay. Also in terms of income, would it be 80 percent of your income?

A Probably more than 80 percent of my income. Probably more something on the lines of in excess of 95 percent of my income. So most of the academic credentials and what I put under the umbrella of academic work, either guest lecturing or serving on other panels, serving as an expert and doing the work, the front work required for those types of activities, that's all being done in my spare time, so to speak.

Q Since you've been employed at Robson, do you have an idea of the percentage of cases that you've reviewed for plaintiffs or injured parties in the litigation?

A Yes, I do.

Q And about what percentage is it?

A You know, the goal is about 50/50. I would estimate a fair estimate that it's probably something on the lines of 60/40, maybe could even be as much as 70/30 plaintiff/respondent, defendant.

Q More plaintiff than defendant?

A More plaintiff than -- correct.

Q You mentioned the fact that you're now an adjunct professor at University of Rochester since

2009, correct?

A Correct.

Q And that's renewed annually?

A Yes, it is.

Q Is that at your request or at Rochester's request?

A Both, but I have to tell you that annual review letter comes religiously without me having to make any phone calls at all. I mean, I have a presence at the University of Rochester. In addition to the duties that I spoke about -- serving on student committees, guest lecturing -- I live near the University of Rochester. I participate.

I maintain that connection and participate in that academic environment, which means that I attend lectures and seminars there dealing with topics of interest in immunology, toxicology, environmental medicine. I attend their functions. You know, I maintain that professional affiliation.

Q Since 2009, since you've become an adjunct professor, have you taught any semester-long classes at the University of Rochester?

A The answer to that is no, and I never taught any semester-long course at the University of Rochester. The only semester-long teaching duties I

had was for a period of time, and it's detailed on my CV, but where I served as course director.

I don't remember if that was over a three- or four-year period of time, but the point I'm making there, it wasn't just a one shot deal of Mike, you're the course director this year and you're done. And that was for a number of courses, for courses that were the core courses for the toxicology students, but also courses that were targeted to immunology and immunotoxicology.

Let me back up because actually I misspoke there. When I said that I never had any semester-long teaching duties that's not true. I never had any semester-long teaching duties where I stood in front of a classroom and had to give lectures on a daily basis.

In graduate programs a lot of the teaching is to a group of students much like the young people who are in the back of the room here where we sit around a table and it's smaller groups and we talk about scientific papers and certain topics. Those oftentimes were semester-long. And those would be topics relevant to immunology and immunotoxicology.

Back to the answer to your question is no. Since I've left University of Rochester I've never had

any semester-long courses that I've participated in. There's one on the table now that I will come back and serve in the capacity I just indicated with small groups of students.

Q When I asked about semester-long, that would include you having a certain role teaching a couple classes part of the semester on a regular basis. Have you had that since 2009 in any particular classes?

A No.

Q I also noted, looking at your CVs, that you're no longer a member of the American Association of Immunologists since 2008. Is that correct?

A Correct.

Q Looking at your CV, is it fair to say that your focus and your research and your publication and your journal editing duties relate more to toxicology than immunology?

A No.

Q Okay. Is it fair to say that the focus of your research and publication and journal editing seems focused more on heavy metal toxicity dealing with lead, mercury and arsenite?

A No.

Q Well, I was looking at your CV, Exhibit 40, the updated CV, and I think I found I counted 39 peer-

reviewed publications, and I counted 32 of them deal with heavy metal issues. Is that fair?

A That's correct.

Q Okay. And I also looked at the list of book chapters on Exhibit 40, your updated CV. It lists 12 book chapters that you've contributed to, and nine of them have dealt with heavy metal issues. Is that correct?

A Yes. So all of these, as I described it earlier, all of these -- not all of these. Most of these publications and book chapters that you are asking me about focus on the bridge between toxicology and immunology.

So certainly, yes, they absolutely have an environmental trigger, a toxicology component to the work, but the endpoint and the outcome is focused on mechanisms within the immune systems, mechanisms of signal transduction -- that's biochemical signaling pathways within cells that are relevant in control and regulation of the immune system -- and all of these are done in the context of consequence, meaning who cares? What does this mean in the context of human disease?

In fact, the one that comes to mind immediately is my grant titles. My work on lead is

focused, was focused and continues to be focused, although I'm not as actively pursuing it, but certainly thinking about and it just doesn't go away that you don't think about these things anymore. But my lead work through the grant was entitled Mechanisms and Consequences of Immune Modulation by Lead, and it's just as I described it before. We're using lead as a tool to provoke changes in the immune response.

Immunologists have been doing this for decades. If there was a card carrying immunologist in the room, and I use terms such as Concanavalin A or endotoxin, lipopolysaccharide as provokers of the immune system. They say oh, yeah. Sure. But I was using environmental chemicals for the two reasons that I said. One is because you could use them as tools to provoke changes in the immune response that you could study and perhaps learn something, and they had environmental relevance because people are exposed to them.

Q Regarding your peer-reviewed publications, looking at Exhibit 40 it appeared that the last one was authored in 2010. Is that correct?

A That's a paper I'm a middle author on. It's a paper that has to do with lead. It's a review paper that has to do with lead in inflammation. Is that the

one?

Q I'm looking at Population Based Assessment of Blood, Blood Levels and Relation to Inflammation, 2010.

A Right. Right.

Q Is that the last peer-reviewed publication that you've had?

A That is the last peer-reviewed publication. I don't put things on my CV until it's been accepted for publication, so that is the last peer-reviewed publication that has been accepted for publication.

Q Okay.

A What I'm saying there is that there are other publications that we're working on, an extension of the work that I was doing and continue to do as a consultant for research that's ongoing at Wayne State University centered on mercury modulation of B cell signaling pathways, but those are all in draft form and will be submitted. But, yes. Absolutely my focus and the necessity for my career to be publishing or perishing has been on a hiatus during this transition period at Robson Forensic.

Q And just another question. Your book chapters. The last book chapter listed on your CV that has been completed is 2010, correct?

A Yes. Correct. Book chapters. I don't know if you've ever had occasion to be asked to write a book chapter, but writing book chapters, that's just a huge undertaking of time and one that -- yeah, I've been asked to write book chapters during this time period, but have actually learned to say no because of the time, because of the time considerations while I'm transitioning in my career.

Q I didn't see anything on your CV regarding any research on arthritis. Is that correct?

A That's correct.

Q I didn't see anything on your CV regarding any research on systemic JIA, correct?

A Correct.

Q And I didn't see anything on your CV regarding any research regarding vaccinations. Is that correct?

A That's correct. There is nothing on my CV regarding vaccinations, but perhaps worth mentioning -- I think worth mentioning so I'll mention it. So earlier I mentioned that I was a member of the environmental health sciences center at University of Rochester, and I described that a little bit. I described the Immunomodulators and Immunopathogenesis Research Core.

This environmental health science center includes investigators not just in environmental, in toxicology, but throughout the University that were like-minded, that had an interest in human disease genetic and environmental factors, including individuals from the Vaccine Biology Department at University of Rochester, as well as Department of Microbiology and others.

I give you that lead-in because there's two things to understand about the academic environment. In addition to being a very strong toxicology program both by research, environmental health science center, NIH supported graduate training program, also a very strong vaccine biology program there.

And given the mission of the environmental health science center, one of the things that it does is to fund pilot projects. One of the pilot projects that I received funding for involved an assessment of vaccine titers in response to Gardasil in lead-intoxicated girls. So it was a very small sample size, a very small -- where the focus again was more on lead and their lead exposure because their lead exposure had been well-documented since childhood, and then to use that as a group to study vaccine responses.

So that work is ongoing. I mean, it's actually work that was ongoing as I transitioned from U of R to Robson. You know, the front end of the work is complete in terms of enrollment, the immunizations being executed, the serum samples being collected. The data needs to be analyzed. So I have participated in research in vaccine-related research. It's not on my CV.

And I don't mean to make great hay out of it, but again to really put it in the context of who I am and what I've been talking about is that the emphasis there is that I viewed that as an opportunity to translate work in animal models and in some culture systems, mechanistic type work, into a descriptive human disease, human response type of a thing.

Q And I know and you mentioned that you testified in the Vaccine Program one other occasion. That was in the Snyder omnibus autism proceedings in November 2007, correct?

A Was it Snyder or Cedillo? Colton Snyder? Colton Snyder? Yes.

Q You testified in that case, correct?

A Yes, I did.

Q And you testified for HHS, correct?

A Department of Justice.

Q Well, yes. Department of Justice. We represent HHS. Respondent is HHS. And the issue that you testified about in that case was concerning mercury toxicology and the thimerosal used in the MMR vaccine, correct?

A It was, but really my recollection and my understanding is what attracted the attorneys from Department of Justice at that time was what I've been talking about here today is that bridge. Here's a guy. Here's a scientist who has an understanding of the immunology, as well as the toxicology, so that was my understanding.

Much of the work I did in that case on the front end was to get at those issues, to address claimant's experts, how claimant experts had put together how mercury influences the immune system and may be contributing to autism, but certainly during the trial my toxicology hat became very prominent because those were the issues that emerged more centrally during the actual proceeding.

Q Have you testified since November 2007 in any legal cases?

A Yes, I have.

Q I found that you testified in June 2011 for a plaintiff in a DWI or DUI -- I'm not sure what they

call it in New York -- related car crash. Is that correct?

A It isn't, but can I explain what the distinction is?

Q Sure.

A It wasn't a DUI case. A DUI case would be a criminal case. I don't have anything to do with the criminal aspect of it. It was a dram shop case.

Q Correct.

A It was a civil procedure.

Q A civil procedure where the issue was serving alcohol to the person who was driving and got into the accident.

A It was an overservice of alcohol issue.

Q And the issues that you testified in that case related to blood alcohol levels, correct?

A By and large, yes.

Q Other than that case in 2011, have you testified in any other Court cases?

A Yes.

Q Okay. And the testimony you've given in other Court cases. Has it been related to toxicology type of issues related to blood alcohol levels?

Let me ask a better question. Some of the cases you've testified in -- well, let me back up and

ask how many cases, if you know, have you testified in since November of 2007?

A Since November of 2007? I'm going to shoot from the hip and say 10 or 12. Something along that.

Q Okay. And of those 10 or 12 cases --

A Let me back up.

Q Sure.

A I'm sorry. In trials, so it's about 50/50 trials and depositions.

Q Okay. Where you've given testimony like we're giving today, about 10 to 12 cases?

A Correct. Either in trial or in deposition.

Q Either in trial or a pretrial deposition?

A Right.

Q Yes? Is that a yes?

A That's a yes.

Q Thanks. And in terms of those 10 to 12 cases, what number of those cases have related to issues concerning blood alcohol levels?

A So the one trial you mentioned for sure and at least one deposition that comes to mind. I'm just drawing a blank. There may be others.

And I'll tell you. I mean, I certainly get contacted a lot. Whether it goes to trial or deposition, I certainly get contacted a lot about

these types of civil cases that involve an analysis of blood alcohol and the fundamental principles of toxicology that are applied in vetting those issues.

Q Have you also testified in litigation concerning DePuy hip replacements?

A I have not testified in those cases, no.

Q Have you given, and I found this series of videos that are online on You Tube, 12 videos. I guess they were posted -- you'll have to excuse me because I'm a little old school -- by a personal injury firm in Sacramento, California, Kershaw, Cutter & Ratinoff.

A Yes.

Q And 12 videos talking about the issues of metal toxicology concerning hip replacements.

A Yes. So the answer is yes. You know, the take-home message, whether they separated it out in the 12 -- I mean, for me it was all live at one time.

But really what the discussion centered around is the same thing that I've been saying here, and that was the reason why those attorneys had asked me to do that, to serve as a resource to understand how cobalt and chromium, as environmental modulators, could be influencing the immune response and what do people need to know and what do they need to

understand in terms of the connection between those degradation products and inflammatory processes.

So there was both a toxicology component to it, as well as a biological response immunology inflammation component to it. So through that video, which I thought long and hard about doing, my view is I didn't express any opinions there, but I was providing information about those two aspects of that issue.

Q And you would agree that Robson Forensic has a section or a portion of its website talking about expertise in ASR hip replacement cases, and you're listed as one of the people --

A They probably do. You know, I don't -- they probably do. I wouldn't be surprised.

MR. WISHARD: Can I show counsel what I printed off the website just so I can familiarize them with it?

THE COURT: Sure.

MR. WISHARD: And I can mark it as the next Respondent exhibit.

THE COURT: Why don't we see how things go, but sure. Show it to Ms. O'Dell.

MR. WISHARD: Absolutely. I believe the next exhibit would be H. I'll have to look, sir. I

can check at the break.

(The document referred to was marked for identification as Respondent's Exhibit No. H.)

MR. WISHARD: May I approach the witness?

THE COURT: Yes.

MR. WISHARD: Thank you. I'm handing Dr. McCabe the next Respondent exhibit.

BY MR. WISHARD:

Q I'll represent to you this is a printout from the Robson website. Are you familiar with this?

A I am.

Q Okay. And this is what I was discussing to you in terms of Robson Forensic advertising expertise in ASR hip replacements and you being one of the experts that they were focused on.

A Correct.

Q Okay.

A And getting back to answering your question of why the change in my CV from toxicologist to immunologist, I think you can appreciate based on some of the questions that you asked me and perhaps put in context my response earlier that when I first came to Robson wearing a toxicology hat and addressing alcohol type cases. Robson Forensic is a forensic engineering

company. There's a lot of crash reconstruction and things like that, so the toxicology aspect of it was something that I was attracted or attracted them to me.

So my practice at Robson Forensic has developed and merged during this time, and during this time period at the same time that the Biomechanical Engineering Group was building at Robson the Depuy hip litigation came along, and my expertise and background dovetailed with that procedure as well.

Q Other than today and in the Snyder case, have you testified in any other cases where a vaccine was involved?

A No.

MR. WISHARD: Special Master, I have no further questions, and I don't object to Dr. McCabe testifying in this Court today on the issues of immunology.

THE COURT: Okay. Dr. McCabe, let me ask you one kind of basic question. When I think about like mercury causing a disease I think of mercury as having like a toxic quality.

I wasn't one of the Special Masters who did the autism cases so I don't know all that much about mercury, but I think about that mercury would almost

be like a poison in a way, but I think what you're telling me is that some environmental chemicals can stimulate an autoimmune response, and I've heard from Special Masters in other cases how an autoimmune response raises the body's immune system. The T cells get misdirected.

So am I right that you're saying that sometimes these environmental exposures lead to an autoimmune disease as opposed to a poisoning where they directly affect the cells, but they can also lead to a disease through the immune system?

THE WITNESS: Yes. And let me just provide you with some insight to that. You know, you hear the word toxicology and you use the word poison, right, and most people have the image of the skull and crossbones, right? You pick up something that's toxic or you look wherever you store your chemicals you'll see the skull and crossbones often times. It's an image that we associate with toxicology.

You'll notice in my professional career at University of Rochester I didn't work at the Department of Toxicology. I worked at the Department of Environmental Medicine. So there's a paradigm shift that's occurred over time that's really applicable to what you're asking me. Toxicology has

evolved to a point that we know about carbon monoxide and how it can kill people.

We know about high doses of environmental chemicals, including mercury or lead and how it can cause death or severe injuries, but environmental medicine, environmental modulators of disease, deals with the more complex issues that are relevant to what we're here today to discuss, which is how does the environment interact with other factors, including genetic factors, to cause idiopathic diseases or what are described as idiopathic diseases. And this is really what my career and my professional activities have been about.

But then back to mercury. Yes, mercury is well known to be a poison in various forms. A fundamental concept in toxicology is that the dose makes the poison, so the level is important, but most people aren't exposed to very high levels of these environmental toxins anymore. We know a lot about that, and toxicology has been successful at responding to that.

That doesn't mean that we're not exposed to background chemicals that can contribute to diseases in complex ways, and that's admittedly difficult to ferret out, but nevertheless worthy of scientific

inquiry, especially during the same time period as our techniques and model systems and things like that have also evolved.

So mercury may be serving as a poison in certain contexts to induce autoimmune disease, but the last thing I want to say here to inform your understanding is don't take it too far. We don't have enough information, for example, that mercury causes human autoimmune diseases, but very good animal model diseases that really illustrate some of the complexity that they've talked about here in terms of an environmental chemical interacting with genetic factors, so there's a very strong genetic component to the animal models of mercury induced autoimmune disease.

THE COURT: All right. With that I think we've completed our review of Dr. McCabe's background, and I'll accept him as an expert in the field of immunology. Ms. O'Dell, do you want to resume your direct examination?

MS. O'DELL: Yes, Your Honor.

DIRECT EXAMINATION RESUMED

BY MS. O'DELL:

Q At this point, Dr. McCabe, let's turn our attention toward Vanessia Koehn and talk about her

background and course just for a few minutes. When was Vanessia born?

A Vanessia's date of birth, as detailed on her birth certificate, Exhibit 1, was February 23, 1995.

Q And prior to June of 2008, what was her general health?

A Her medical records indicate that she was healthy. No indication of any chronic disease. I believe that's Exhibit 5, page 20; Exhibit 4, page 9. And what I mean by that, I think those are from health histories that were taken where those exact types of statements were made, that this is a well child and no background of any chronic diseases or anything of that nature.

Q Dr. McCabe, what is Gardasil? Explain that for us just generally and then the number of shots required and the schedule of those shots as recommended.

A Gardasil is a vaccine. It's a human papillomavirus vaccine manufactured by Merck. It's a recombinant vaccine, meaning that it's a subunit vaccine that is synthesized and put together in yeast cells. The subunit happens to be the human papillomavirus capsid protein. It's the capsid protein that is the outer face of the virus or the

virion that interacts with receptors on cells to allow a virus, a DNA virus like HPV, to gain entry to the cells.

So Gardasil is a recombinant quadrivalent vaccine, quadrivalent meaning that there are different strains of human papillomavirus, and this is a vaccine that contains the four main strains of HPV that have been implicated in human disease either in genital warts or in ovarian cancer, and the four subunits are HPV-6, the L-11 protein from the HPV-6, -11, -16 and -18 viruses.

It is, as I mentioned, manufactured by Merck with a schedule through their clinical trials and other research. The schedule for delivering the vaccine is an initial shot, a second shot two months later and then a third shot at six months. So zero, two months, six months.

Q Tell us, Dr. McCabe, what cancer is Gardasil indicated --

A I'm sorry. I said ovarian. I mean cervical cancer.

Q Okay. And did Vanessia receive the full course of Gardasil shots?

A Yes, she did.

Q And tell us what dates she received those

shots.

A Vanessia received the first of the three-part vaccine on February 18, 2008. That's Exhibit 2, page 3. The second and third doses of Gardasil were administered according to the immunization schedule almost spot on, April 18. So that's the two month shot, April 18, 2008. I believe that also is Exhibit 2, page 3 or 4, and the third shot was administered on August 19, 2008.

Q All right. And prior to this time had Vanessia received other vaccinations?

A I'm sorry. Ask me that question again.

Q Prior to this time, prior to --

A Prior to that time she did receive other vaccinations. My recollection is that her immunization record was complete. She had never had -- no indication in the medical records that she had ever had a prior adverse reaction to any of the vaccines or complications from any of the immunizations that she had received, and that is contained in Exhibit 3, pages 3 through 5.

Q After the first Gardasil shot, did Vanessia have any difficulties?

A None that are documented in her medical records or anything else that I reviewed.

Q When did she begin having difficulty? Well, let me ask you this. Did she start having difficulties after the second Gardasil shot?

A Yes. Between the second and the third in time she did start having some problems.

Q When was the onset of her symptoms?

A Mid-June was the onset of her symptoms. I believe it's been documented June 21, 2008, she had developed a rash all over her body.

Q Okay. And following the presentation of that rash, did Vanessia seek medical treatment, and what was her course of treatment after that time?

A She did, and I believe it's on June 24 she went to her primary care physician, Dr. Ragala, and at that time she had presented to Dr. Ragala with the complaint of the rash, and Dr. Ragala had suspected that it was some kind of an allergic reaction and provided her with Benadryl. And that information is documented to my understanding, as I have it in my report, Exhibit 3, page 8, and Exhibit 5, page 51.

Q And what happened after her treatment with Benadryl?

A The Benadryl was not effective. It didn't solve the problem. In fact, a short time thereafter, something in the timeframe of perhaps June 24, I

believe, she developed in addition to the rash developed or presented with joint pain, fever and severe pain in multiple joints.

Q Did she seek treatment at a hospital?

A She did, and I believe it's in the record, Exhibit 4, June 28. She began her treatment and diagnosis, clinical workup, at Marian Medical Center.

Q And as a part of the clinical workup at Marian Medical Center, was bloodwork performed?

A Yeah. Bloodwork and diagnostic tests were performed, and that included, as you asked me, bloodwork that included analysis of and findings of elevated markers of inflammation, including an acute phase reactant protein, C-reactive protein, elevated sed, erythrocyte sedimentation, which is also an indication of inflammation.

Her neutrophils were elevated. Her platelets were elevated, and she had a number of other markers that were also found to be elevated that were indicative of an inflammatory response. At the time she was also presenting with rash, fever and joint pain.

Q Specifically, Dr. McCabe, what was Vanessia's C-reactive protein level, and how did that compare to the upper limit of normal? And if you

would please give us the exhibit and page number in your answer?

A Exhibit 4, page 32. Her sed rate was 23, so elevated over the reference of zero to 20. Her white blood cell count was elevated. Again, this is on Exhibit 4, page 32, and these were tests that were conducted on June 28 and June 30. Her C-reactive protein determined on June 28 was above two, so about four times higher than the reference range. Her platelets. Her platelet counts were also elevated, in the 500s, and her neutrophils were elevated.

Q Dr. McCabe, was additional bloodwork done following the bloodwork that you testified to on July (sic) 28 and 30?

A Sure. So she was in the hospital. My understanding is she was in the hospital at Marian Medical Center during that time period, and tests conducted on July 1 showed that her sed rate had increased to 46. Her neutrophils and platelets have remained elevated. She still had a high white blood count.

Q Was she examined by a rheumatologist at that time during her hospital stay at Marian Medical Center?

A Yeah, I believe she was. I believe she was

seen by Dr. Scott during that timeframe, who was a rheumatologist. My understanding is he's a rheumatologist.

Q And what was Dr. Scott's diagnosis?

A His diagnosis was he suspected that she was suffering from systemic juvenile idiopathic arthritis.

Q And what medications were started at that time?

A She was started on Prednisone and Naproxen.

Q And in following Vanessia's discharge from Marian Medical Center, what was her course of treatment?

A Her next course of treatment was in association with the UCLA Pediatric Rheumatology Group.

Q And who was her treating physician?

A Sorry. I'm drawing a blank on that.

Q Does Dr. McCurdy ring a bell?

A Dr. McCurdy, yes. Dr. Deborah McCurdy. Thank you.

Q Okay. And was Dr. McCurdy's diagnosis consistent with Dr. Scott's?

A As I understood it, yes, it was. Her diagnosis was that Vanessia had developed systemic juvenile idiopathic arthritis.

Q You testified just a few minutes ago that Vanessia received the third shot of Gardasil on August 19, 2008. How did she respond following the third shot?

A Clarify for me what you mean by how did she respond.

Q Did her condition worsen following the third shot of Gardasil?

A Well, whether it worsened or not, I mean, the record does document that she developed a rash that she hadn't had since March.

She was described as having a flare, an increase or exacerbation of her joint pain in both her knees and ankles, shoulders and wrists, so polyarthralgia, and there was some documentation, as I recall, from PT that she wasn't able to participate in her physical therapy sessions because of her complaints.

Q Okay. And to your understanding, is Vanessia under the care of a rheumatologist today?

A Yes, she is. My understanding is and my recollection is that she remains under the care of Dr. McCurdy.

Q And what are her current medications, according to the last medical records?

A According to the last medical records that I recall seeing, she remains on Methotrexate, Enbrel, a TNF alpha inhibitor, and folate to control the toxicity of Methotrexate.

MS. O'DELL: Okay. Your Honor, at this point we're going to transition into another subject matter. I don't know what Your Honor's preference is for a break. We've been going about an hour and 20 minutes. I'm happy to continue on, but if you break at an hour and a half this might be a good point in time.

THE COURT: I'm okay with going forward, but if anyone else wants a break, we can keep going.

MR. WISHARD: We're good to go.

THE COURT: Okay. So maybe we can maybe shoot for around two hours or so.

MS. O'DELL: Okay.

THE COURT: Maybe another half an hour or so.

MS. O'DELL: Yes, sir. That would be fine.

THE COURT: But if anyone needs one more urgently than that, just raise your hand.

MS. O'DELL: Okay. All right. Very good.

BY MS. O'DELL:

Q Okay. Well, at this point in time, Dr.

McCabe, let's transition and discuss systemic JIA. In particular, describe for us, please, the disease systemic JIA or juvenile idiopathic arthritis.

A There's a slide to change, I think.

Q Sorry. Thank you.

A I have a number of references documented in my report and a few slides here of figures that I extracted from those references to assist us -- assist me -- and assist your understanding of SJIA as I understand it and so I'll refer to those and also to my report.

Q Dr. McCabe, can I just interrupt you for a minute?

A Sure.

Q Would you describe for us, please, a classic presentation of systemic JIA?

A Yeah. The classic disease presentation includes recent onset fever, rash, joint pain, together with systemic elevation of inflammatory markers that are all indicative of an autoinflammatory condition. So systemic juvenile idiopathic arthritis is understood to be an autoinflammatory condition.

Q Okay. And compare for us systemic juvenile idiopathic arthritis to juvenile idiopathic arthritis.

A My understanding, and I think for my

understanding the key distinction is in systemic juvenile idiopathic arthritis the presentation involves what I just said, systemic markers, changes in inflammatory markers in blood and presentation with a fever and rash, so systemic meaning all over the body, whereas juvenile idiopathic arthritis is limited to the joints.

Q Okay. And what do scientists think are the contributing factors for the cause of JIA?

A It's documented. We'll start with this slide, and I've got a pointer here that's not working on that slide, but over in the top -- that's interesting. Oh, there it is. Okay. It works there, but it doesn't work there. There we go. A little technical issue.

Q Yes.

A As I mentioned, I have a few exhibits to assist with this that I hope will provide some clarity. This is a figure that's taken from the Prakken article, which is Exhibit --

Q 12.

A -- Exhibit 12. And I believe this is Figure 1. It was actually centered on JIA, not systemic JIA, but I think useful to start this discussion. One of the Special Master's questions at the beginning was in

these articles it's not clear whether it's JIA or SJIA or referring specifically to JIA as I just described it as a disease limited to the joint and immunological inflammatory reactions occurring in the joint or whether these articles are referring generally to JIA.

I think the answer is both, depending on the context of the individual articles and where you are in the article at the time, but I think from my perspective as I understand it it's as I said. Systemic JIA is a systemic disease, whereas JIA is limited to the joints. And some of the things that I've read and have an understanding for is that SJIA is considered to be a subtype of JIA. Whether or not that's exactly true or not I think is a matter of debate and evolving science.

So this is a cartoon on JIA, and in the center part there, whether my marker works or not, in the center part there you see tissue damage and expression of autoantigens, and that's correct in the context of JIA limited to the joint because that's the business end of where the disease is occurring, and that's what's of interest here. What's applicable both to JIA and SJIA that we can take away from this cartoon is that there is a I think scientific consensus that this is a complex disease that involves

or complex collection of diseases that involve disregulation of various immunological events.

They are viewed to be autoinflammatory diseases, meaning that at the top of the screen around 11 o'clock that release of DAMPs, which stands for damage associated molecular pattern molecules, essentially innate signaling, as well as proinflammatory cytokines as listed there -- TNF, interleukin-6, but also interleukin-1 and interleukin-18 -- are the mediators of the disease process certainly in SJIA, but also in JIA, as those mediators of the innate immune system interact with elements of the adaptive immune system as the adaptive immune system players being exemplified in this cartoon starting around five o'clock, around eight o'clock.

The other reason I think this is a useful article to start our discussion is that it emphasizes both in the cartoon, as well as in the article itself, that there's an understanding and belief based on science and medical research to date that there are genetic susceptibility factors, as well as environmental triggers, working in concert to drive these diseases.

Q And would a vaccine be considered an

environmental trigger?

A Sure. So vaccines would be environmental triggers. Infections are environmental triggers. Environmental chemicals and drugs are environmental triggers.

Q Explain for us, please, what is meant by the disregulation of the innate immune system.

A That's going to come out. I actually have a cartoon I think that would help with that if we can -- I don't mean not to answer your question, but let me answer it quickly here. Actually ask me the question again because the first thing I thought of is that we're out of sequence, but go ahead.

Q Okay. What's meant by the disregulation of the innate immune system?

A So you're asking me what -- first, for you to understand disregulation of the innate immune system I think you need to understand what the innate immune system is. I added an article in May, the Gregersen article, and I have some exhibits from this that we'll talk about in a few minutes. And Gregersen -- is it Exhibit 40?

Q It's Exhibit 36.

A Sorry. Exhibit 36. This is an article by Gregersen entitled Genetics of Autoimmune Disease,

Disorders of Immune Homeostasis, and what Gregersen does in this article is very nice. In the left-hand -- I'll give everybody a minute to catch up if you want to be able to follow along. In the left-hand side of the margin he defines terms. And so the innate immune system. What does innate mean? Well, innate means it's inborn. And when we talk about innate, to really understand it you have to understand that it's a compare and contrast, innate immunity to adaptive immunity.

The innate immune response is more primitive evolutionarily, so it's phylogenetically ancient. In comparison to the adaptive immune system, it's more nonspecific, and it's more nonspecific because the receptors that are present on cells of the innate immune system, which include macrophages, neutrophils, are less specific and have less flexibility in recognizing foreign antigens than the receptors that are present on cells of the adaptive immune system, which is a realm of lymphocytes. When we talk about receptors on lymphocytes, we're talking about antigen receptors, T cell receptors and B cell receptors.

Important to understand is that the innate immune system and the adaptive immune system interact, so while it's useful to categorize, and immunologists

do this all the time to improve understanding, but again don't take it too far to a reductionist approach so that it becomes less functional to explain immunological mechanisms and disease mechanisms.

Immunologists do it all the time that they categorize things into a pile, innate immunity versus adaptive immunity, but the innate immune system and the adaptive immune system interact continuously in nearly every immune response, whether it be an immune response to an infection, to a vaccine, in an autoinflammatory or an autoimmune disease process where the response is directed at autoantigens.

So then what disregulation of innate immunity means by virtue of what I just explained to you, this interaction between innate immunity and adaptive immunity, is that the image to conjure up, the thing to understand, is that there is balance. The immune system is all about balance response.

There's an infection. That's a threat to self. It's danger. That's why DAMPs are named danger -- damage or danger -- associated molecular pattern molecules. There's a danger that the host needs to respond to, and it's the immune system that's charged with responding to that, and it has to do it in a balanced fashion. Get in. Get out. Take care of the

infection. Take care of whatever the bad actor is. And then inherent in the immune response is to turn that off.

And there's many sophisticated cellular and biochemical and molecular mechanisms that immunologists have defined and understood through research throughout -- certainly the last few decades has been very fruitful in immunology research. So the disregulation is tipping that balance.

Q And tell us. The Prakken figure that's here. Outline for us the balance that is described in that figure.

A Well, the balance that's outlined in that figure is down in the lower right side. What is that? Four o'clock? Five o'clock? And around the horn here is again, this is the concept of categorization within the immune system. You know, I talked about B cells and I talked about T cells. Well, then there's subsets and subcategories of T cells. There's T helper cells that regulate adaptive immunity. There's suppressor cells or back in the '70s and '80s what were described as suppressor cells. Now terminology calls them regulatory cells.

But the concept is still the same is that these are cells that exist to help turn off or temper

the throttle on the adaptive immune response to an infectious agent. So in this figure, one of the immunoregulatory processes that is in place is activation of these T regulatory cells that are charged with turning off -- which function to turn off immune responses, and they do so by production of cytokines.

Q Okay. And what are some of the specific cytokines that are referenced in this figure?

A Well, the reference in this figure, I hope I alluded to that already. But in the afferent, the coming in side of the response and contributing, initiating part of the disease, proinflammatory cytokines drive the disease and are considered to be important, and those include TNF, interleukin-6, not referencing this figure, but within the same category, interleukin-1 and interleukin-18.

And you'll see that. You know, I know it's not referenced in this figure, but certainly I didn't just include one figure and cite one paper in building this argument or supporting this argument today that there are additional reviews and research that weigh in on this that indeed demonstrate that other proinflammatory cytokines other than the ones that are listed here are implicated in the disease.

Q In your opinion, was Vanessia exposed to an environmental trigger?

A Yes, she was.

Q And what was that trigger?

A I believe it was the Gardasil vaccine.

Q And what is your opinion in regard to why Gardasil was an environmental trigger?

A I think there's three elements that I'll touch on for that opinion. Some of those may have subelements, but here goes. The first element is that Gardasil elicits the production of proinflammatory cytokines, many of the ones that I've just mentioned, that have been strongly implicated in both the development and the progression of systemic juvenile idiopathic arthritis. So that's one.

Two is that there's an obvious temporal association between Vanessia Koehn's vaccination with Gardasil and her symptoms and diagnosis with SJIA and the interval of time between her vaccinations and the onset of the symptoms, the presentation and onset of the symptoms of this autoinflammatory disease process is predictable by the time period when immune responses are seen to be induced by the vaccine.

The third elements is that Vanessia Koehn's vaccination with Gardasil was a substantial

contributing cause of her development and progression of systemic juvenile idiopathic arthritis as evidenced by her medical records, which document clinical markers and clinical presentation indicative of elevated proinflammatory cytokines.

So her fever, her elevated C-reactive protein, acute phase reactive proteins, the rash. These are all effector functions or consequences, clinical manifestations of proinflammatory cytokines, chiefly interleukin-6 and interleukin-1, as well as TNF alpha.

The scientific and medical literature supports this conclusion that connects Gardasil and systemic juvenile idiopathic arthritis by a common mediator of the disease process, an element of the disease, namely these proinflammatory cytokines, and this is supported by her clinical improvement upon receiving therapies that target the activity levels of these same proinflammatory cytokines.

And I think my opinion is and shared in published literature is that the best way to prove that proinflammatory cytokines are involved in a disease process is to inhibit their activities. This is a fundamental paradigm in research. It dates back to Koch, K-O-C-H, and Koch is postulate.

Some people pronounce that Koch is postulate. Koch is postulate, and one of Koch's postulates -- Koch was a microbiologist -- is how do you prove that A causes B, and one way to do it is to come up with an inhibitor or some way to interfere with that process. That's one of Koch's postulates. I think there were four of them.

And that's what's at play here. At the fundamental level, remove the proinflammatory cytokines and the activities of those proinflammatory cytokines by coming up with an inhibitor, something that either targets the cytokine itself, targets the cytokine receptor or targets the cytokine receptor pathways or pathways to turn those cytokines on.

Q In addition to the Prakken article, what other scientific publications support your opinion in that regard?

A Well, the ones that I cited are detailed in my report. I believe they're Exhibits 12 through 14. Sorry. Exhibits 12 through 14. There's the Prakken article. I believe that's Exhibit 12. Am I right about that?

Q That's right.

A Okay. And then Exhibit 13 is the Mellins article, and Exhibit 14 is an article by Martini.

I've talked about Prakken. I'm not necessarily going to talk about Martini. It's just value added. But I would like to talk about Mellins for a few minutes.

Q Tell us about that.

A So Mellins, this is an article that's focused on systemic juvenile idiopathic arthritis by virtue of the title. This is good science. This is what science is about. Some answers, more questions, is embedded right in the title. And so some answers are provided from it, and this is what scientists do all the time. They make hypotheses, find some answers, maybe modify their experimental approaches and generate more questions.

Mellins's article very nicely details some key points for us to think about in the context of what we're here today to talk about and things I've already talked about. There's a contribution of the innate immune response to systemic juvenile idiopathic arthritis. That's what's prominent. That's where in the last five years or so much of the research emphasis has focused on understanding the role of the innate immune response and proinflammatory cytokines in the etiology of this disease. There's also mention it's been a shift in general immunology during this same timeframe, generally speaking.

Within this timeframe also has been the emergence of the concept of autoinflammatory disorders, and we'll talk a little bit more about that perhaps in a few minutes, but there's a classification of systemic JIA as an autoinflammatory disorder, meaning that you can conceptually think about autoinflammatory disorders in the context of the innate immune response, as I discussed earlier.

Much data suggests that systemic JIA has genetic factors, as detailed or discussed in the figure from Prakken, so it's a multigenic disease, multiple genes, meaning that certain susceptible members of the population likely exist and develop this disease with or without environmental triggers. It has a connection to macrophage activation syndrome. I'll talk a little bit about that perhaps later.

Proinflammatory cytokines, including IL-1, but also IL-6, TNF alpha, are critical proinflammatory cytokines in systemic juvenile idiopathic arthritis, and it's really these proinflammatory cytokines and, as indicated here, interleukin-1 that's driving the disease in initiated individuals. Interleukin-1. It's interleukin-1.

It was the first cytokine that was discovered, characterized back in the '70s and '80s,

to describe interactions. Interleukin, leukin meaning leukocytes, so this is a protein chemical messenger that communicates between cells of the immune system. It's a cytokine produced by macrophages and exemplifies the cross-talk between the innate immune system and the adaptive immune system that I discussed earlier.

So here we have a cytokine, interleukin-1, produced by macrophages that regulates and functions in a lot of different things, one of which is helping to drive and activate T cells and B cells in the adaptive immune response. But also when interleukin-1 was discovered it was realized that it was a pyrogen. It was the pyrogenic factor that immunologists at the time had been dealing with and trying to understand.

What does a pyrogen mean? A pyrogen means that it induces fever. So interleukin-1, like many cytokines, has pleiotropic -- many, pleio; tropic, tissues, targets. Many targets within the body, meaning it acts on other lymphocytes, as I indicated. It acts on other elements of the innate immune response. It acts on the hypothalamus to control body temperature. That's where the fever comes from. It acts on the liver to cause the release of acute phase reactive proteins, C-reactive protein as we've

discussed. So this is a cytokine that is critical in systemic JIA, but also has many functions within the immune system, some of which are pertinent to its critical role in this disease.

There's a couple other bullets here just to cover briefly. Now, this article goes into active disease and mediators of both inflammatory and anti-inflammatory pathways being detected, so again you see this categorization or this ying and this yang, turn on/turn off. That's what's meant by regulation or disregulation. This is an inherent -- and by this I mean both inflammatory and anti-inflammatory properties is an inherent part of immunity and how the immune system works, and when that gets disregulated we have problems.

I call this part of the article out more for my background, to address something about my background, than the straight and narrow to describe the disease. But, you know, this concept of alternative activation of macrophages, monocytes and macrophages, has been an emerging concept, really something that came on the line again within the last five years. It may have been in the literature earlier than that, but it's one of those concepts that really has a place everywhere.

And with my lead work, as I mentioned, my lead work and using lead as a tool to modify the immune response. For years we were studying influences of lead on adaptive immune responses, and it became apparent to us during that time period that something was going on in the innate immune system and that lead is differentially affecting the M-1 and M-2 macrophages that are discussed in this article.

Mr. Wishard asked me about the DePuy litigation. Well, in addition to the litigation I should also add that my work and my interest in that area, in addition to the video that we talked about earlier, has involved collaboration and interaction with scientists in the orthopaedic community, and this issue of cobalt as a debris product causing inflammatory changes in the very implant region of those who are having problems, the emerging research in that has everything to do with cobalt modifying M-1 and M-2 populations. So these are concepts that are broad in many aspects of immunology.

I want to go on now from this figure to the next one, which will be somewhat of a review for some of the concepts that I talked about from the figure that I took from Prakken. Also, this is still Exhibit 13. This is something I discussed in my report and

something that I'll discuss here.

What this figure does is it -- let's start with the center. So in the center we have this list of proinflammatory cytokines that have been implicated in SJIA -- interleukin-6, TNF, macrophage colony stimulating factor, interleukin-1 and interleukin-18. Interleukin-18 is a member of the interleukin-1 family, so interleukin-1 and interleukin-18 behave very much the same way.

As I told you earlier, interleukin-1 has effects, as do many of these proinflammatory cytokines, including interleukin-6, on a variety of targets around the body, both within the immune system and outside the "adaptive immune system," but this includes the hypothalamus, producing fever, the liver, activation of acute phase proteins, so this part of the slide is relevant to Vanessia Koehn because she's presenting with these aspects of fever, elevated C-reactive proteins, activated or increased platelets, activated neutrophils and increased neutrophils.

And so although cytokines were not directly measured in Vanessia before/after vaccination with Gardasil, at no time that I saw during the course of her systemic JIA, it's predictable that based on her presentation and some of her bloodwork and diagnostic

indicators that proinflammatory cytokines were driving these processes.

So that's starting from the middle and restating that these proinflammatory cytokines are front and center in the development and progression of the disease and produce these outcome, and then on the top side is just a little bit more consideration of the biology and the immunobiology, the mechanisms that drive the production of these cytokines.

So down here, this is the clinical side. This is what the clinician sees. Up here, this is what the researcher is focused on. I've been a researcher studying signaling pathways all my life. I haven't studied TL, toll-like receptor signaling, but the paradigm is the same. This is the process of signal transduction.

I've got a lot of publications and spent most of my professional career and continue to spend that part of my professional career analyzing these complex events and how information received outside the cell in the outer world -- we've got an infection -- is translated, transduced through the cytoplasm into the nucleus to affect changes. And these are the toll receptor signaling pathways that are discussed in the Prakken article.

And the other point to make here is that when we talk about genetic markers of the disease oftentimes it's complex and there's multiple contributors to the process, so we have genetic changes or genetic susceptibility factors, alleles or differences in genotype at the level of the cytokines themselves, at the level of the cytokine receptors that provoke these changes, at the level of the signaling pathway that leads to the synthesis of these cytokines.

And the point to make here is that many of the genetic predisposition that's been implicated in systemic juvenile idiopathic arthritis are within these pathways or somehow connected to the cytokine biology.

Q Okay. In another article -- Your Honor, this might be --

THE COURT: Ms. O'Dell, let me just narrate for a moment that Dr. McCabe's most recent testimony was about Slide 5 of the PowerPoint. You haven't always given the reference to the PowerPoint slide so that when we go to the transcript we want to be able to marry it up to the right page of the slideshow.

MS. O'DELL: I see, Your Honor. Yes. In the last few minutes he's testified to Exhibit 38/4 and then 5. That's correct, Your Honor.

Your Honor, would it be appropriate if we could take a short break? I would appreciate the Court accommodating that.

THE COURT: Sure. We can go off the record.

(Whereupon, a short recess was taken.)

THE COURT: We'll go back on the record. Ms. O'Dell, where are we going to pick back up? Are we still on Slide 5?

MS. O'DELL: No, Your Honor. We're going to transition to --

THE COURT: Okay.

MS. O'DELL: -- a new topic.

THE COURT: Okay. Good.

BY MS. O'DELL:

Q All right. There's been some question, Dr. McCabe, in this case about whether systemic juvenile idiopathic arthritis is an autoimmune or an autoinflammatory disease. How would you respond to that question?

A Systemic juvenile idiopathic -- SJIA is an autoinflammatory disease by contemporary thinking, but I think some clarity in this concept of autoimmune versus autoinflammatory deserves some attention here. So I'll go through this quickly, I hope.

This constitutes a broad spectrum of diseases characterized by defective immune involvement. Nothing special about autoimmune diseases in general other than that the target antigen is to self as opposed to nonself. It's about the disregulation of the immune response in many of the same immune mechanisms that are in place to protect us, to afford protective immunity.

The term autoimmune conjures up relatively more adaptive immune involvement whereas autoinflammatory relatively more innate immune involvement. So as I say in Bullet 1, this is a broad spectrum of diseases, and as I've told you earlier and am about to tell you in a little bit more detail, there is this concept of interaction and not just a concept, but plenty of examples in immunology, in basic immunology, clinical immunology, where this cross-talk between adaptive immunity and innate immunity is the norm.

So again, this is another example where categorization is useful, meaning categorization into autoimmune versus autoinflammatory. Adaptive/innate is useful, but only useful if it's not put in a reductionist slant and the underlying immunobiological principles are appreciated. And so that's what I want

to comment. This was Figure 6, I believe.

And now Figure 7, and again this is from the Gregersen article, and there's this categorization, as I explained briefly earlier, about adaptive immune and innate immune responses, and this concept in the middle here of the interactions or the interface or the overlap.

I defined for you innate immunity and adaptive immunity. I'll do it again here in a second, but that's a categorization. I want to orient you to think about another two-prong kind of thing to think about. In immunity, immune response is about two general aspects, recognition and response. There's a foreign antigen that the host encounters. The host needs to recognize it, and then it needs to get rid of it. So number one, recognize. Number two, get rid of.

The getting rid of, immunologists, we call these effector functions. Some of those effector functions are detailed here. The recognition events in the adaptive immune response, which is more specific, involves antigen specific receptors, the T cell receptor on T cells, the B cell receptor on B cells.

We have -- humans, mammalians, animals -- a

repertoire of millions of possibilities of putting together receptors -- by putting together I mean by molecular events that occur during development, as well as during an immune response -- to put together these millions of receptors that individual cells, which we call clones, will then respond to upon challenge.

So the repertoire exists and so, for example, the repertoire exists for these recognition events, and there's great diversity in that repertoire and there's specificity in that repertoire. What does specificity mean? In the context of recognition it means that when someone is immunized with polio virus the expectation is that the adaptive immune response will respond to that and produce effectors, antibodies that will respond to polio. It won't respond to measles because the response is specific for polio. That's all the realm of adaptive immunity.

Another way, based on some things that we've talked about and will be talking about here, for you to understand and appreciate this great diversity is that you've heard me mention inhibitors of the proinflammatory cytokines and the use of these therapeutic agents. Many of these therapeutic agents are antibodies to those very cytokines.

So that's from laboratory procedures to produce an antibody, for example, to interleukin-6 that can then be used therapeutically because it's going to interfere with the activities of that particular protein, but it's the very same mechanisms that are in action when a B cell with T cell help responds to produce an antibody to a pathogen or a B cell loses its regulation and produces autoantibodies to self-antigens in an autoimmune disease. So I hope I've described for you the concept of recognition in the context of adaptive immunity.

In innate immunity, recognition is much more primitive, nowhere near the level of specificity that occurs in the adaptive immune response and in lymphocytes, but recognition is still important in the innate immune response, and the recognition is to conserved proteins that are expressed by bacteria, viruses, damaging agents, cellular debris and cellular damaging agents to activate the activities of the cells of the innate immune system, which on the left side of the slide is chiefly to macrophages.

In the macrophage activation syndrome that was discussed it's through those processes, through those recognition events, that the macrophages are being activated. So the devil in the details are very

different, but conceptually in comparing innate immunity to adaptive immunity at that level we're talking about recognition. So now there's a variety of effector functions that deal with that second part of immunity that I told you about.

It's really in these effector functions that this immune innate -- sorry. Adaptive immune/innate immune interface is most illustrative, and there's plenty of examples of that shown on this slide.

Q And just for the record, the slide appears at Exhibit 38, page 7, I believe. And in what article is this figure found?

A This is from the reference is here, Gregersen and Behrens, Nature Review Genetics, 2006.

MS. O'DELL: Okay. For the record, Exhibit 36, Your Honor.

BY MS. O'DELL:

Q Okay. Please continue.

A So an effector function and regulation of the response. Also in effector functions we're dealing with the regulatory aspects of these responses. So, for example, the macrophages. If I point here can you -- if I point on this one?

THE COURT: The court reporter will tell us.

THE WITNESS: I don't know. That's not

going to be effective, so I'm going to stay on the left side where the macrophages are.

Macrophages become activated by a variety of ways, one of which would be through a recognition event that I just described, and produce interleukin-1. And in the top portion there I think there's at least some semblance of a cartoon that shows by those macrophage mediated derived cytokines like interleukin-1 there's cross-talk with cells of the adaptive immune system -- for example, T cells as well as B cells -- to help drive the production of cytokines.

In order for T cells to become activated, and by that I mean recognize a foreign agent or, for that matter, even a self-agent, they need to interact with other cell types, which we call antigen presenting cells. Sometimes those antigen presenting cells are cells derived from the "innate immune system," and sometimes it can be macrophages. Sometimes it can be dendritic cells. Sometimes it can be other cell types. So just on those recognition events and in revving the system up to respond there's clear interactions between the innate immune system and the adaptive immune system.

Coming back the other way now, so in

circumstances where we'll have a B cell will produce antibodies, many of the immune effector functions that those antibodies perform involve interaction with cells of the innate immune system. So, for example, serum proteins complement, some of which are derived from liver cells, some of which are derived from macrophages, once an antibody binds to its target -- for example, a bacterial cell -- that's the recognition event.

But now we need to get rid of that bacteria cell, don't we? And the way the immune system does that is by activation of this complement protein cascade that affects the lysis of that bacteria cell, for example, only in the presence of antibodies, at least in the example that I'm describing.

Sometimes the antibodies bind to a target like a virus and need to be cleared by phagocytic cells, so one of the properties of cells of the innate immune system is that they're phagocytic, meaning they gobble up other things and chew them up and fragment the proteins and that's what's happening, and that's how the innate cells and those phagocytes get rid of whatever the bad actor or pathogen or whatever it may be that the host has been challenged with. Oftentimes that occurs and is facilitated by an antibody that

binds to the pathogen or some other antigen and then interacts through the antibody to facilitate the removal by macrophages.

So these are just several examples of what I've said here and in the context of be careful about stratifying autoimmune, autoinflammatory, adaptive, innate too far because there's interactions, and it occurs at the level of the basic biology, as well as manifestation of disease.

We also have cross-talk between adaptive immunity and innate immunity at the level of cytokines and proinflammatory cytokines, and a good example of that is that in many of the adjuvants that are included in vaccinations the purpose of those adjuvants is to drive innate immune mechanisms, proinflammatory cytokines, and to facilitate these cytokines helping drive the adaptive immune response.

This occurs in the Gardasil vaccine either by virtue of the aluminum hydroxyphosphate sulfate adjuvant that's present in the vaccine, as well as the L-1 capsid protein itself having some adjuvancy properties.

BY MS. O'DELL:

Q So if you would just summarize please, Dr. McCabe, why is this relevant, this interface between

adaptive immune and innate immune systems?

A Well, it's relevant. It's relevant because inasmuch as we can think of, we can conceptualize systemic juvenile idiopathic arthritis as an autoinflammatory disease, in my view I think well, that's a -- when I hear autoinflammatory disease or I think about autoinflammatory mechanisms I think about the innate immune response being prominent.

But I also think, given my understanding of how the immune system works, that well, that doesn't mean that there's no adaptive immune component, and it would be incorrect to refer to this as an autoimmune disease. Perhaps more precise at this point in time to refer to it as an autoinflammatory disease.

Q And just to --

A Actually, I actually would like to add one more thing to that. You have to understand, or I think it would be useful to understand, where did the term autoinflammatory come from? And the term autoinflammatory came from an understanding of single gene defects within cytokines within the innate immune system that produced diseases, autoinflammatory diseases.

These are rare diseases that are not the norm, and it is from those studies and from

understanding of those diseases, which at the same time this concept of integration between the adaptive and innate immune system became more appreciated, that the consideration that there are other autoimmune diseases that are not single gene defects, but are polygenic and also involve environmental triggers, became something to discuss and think about.

Q Is systemic JIA as an autoinflammatory disease process driven by proinflammatory cytokines?

A My understanding is yes, it is, chiefly interleukin-1, interleukin-6, TNF alpha and interleukin-18.

Q In addition to this question of autoimmune versus autoinflammatory disease, another issue that's arisen in this case relates to the Gardasil vaccine versus the natural infection and what effect the vaccine versus the natural infection has on the immune system. Dr. Rose in his report has made much of the fact that no arthritis has been described or associated with natural infection or the natural HPV virus. Is that relevant?

A In my opinion, no, it's not relevant. It's a reasonable place to start in considering a connection between the two, but given the apples and oranges comparison and difference between the immune

response at many levels to HPV infection versus HPV vaccine, that's the basis of my opinion that it's not relevant.

And that's an opinion, that's my stated opinion, and a basis of my opinion, education and training, et cetera, but also the scientific medical literature and some of those references are listed here, and this is Slide No. 8.

Q And tell us, Dr. McCabe, what proteins in the virus are not a part of the --

A I think it's easier -- as much as I remember papillomavirus, some aspects of papillomavirus from graduate school and my virology courses, it is a DNA virus, a double-stranded DNA virus that contains a number of proteins that are both on the surface of the virus, as well as within the viral particle.

The capsid proteins are what the natural infection and the virus share, so that's the L-1 capsid protein, which is the ligand that binds to receptors facilitating viral entry, but there's many proteins that make up HPV virus that are involved in the replication of the virus, that are involved in establishing the latency of the virus, latency meaning that the virus can hide out intracellularly. These are all tied. These concepts are all tied to the

mechanism of carcinogenesis of this particular virus.

Certain viral proteins such as the E-6 and E-7 proteins, which are part of the virion in an HPV infection that are not contained in the vaccine, so the E-6 and E-7 proteins have been implicated in the carcinogenesis process and also been implicated as inhibitors of cytokine responses in HPV infection.

So if I could in answering this question go to the next slide, which is -- well, actually the next slide is Slide 9, which is just the cover, title and authors of the next paper or a table that I adapted from this article. So the author is Mariani, M-A-R-I-A-N-I, and it's one of several papers that I cited discussing HPV vaccine and the immune response to HPV vaccine, as well as HPV infection.

So that would be then -- am I tracking right -- this is now page 10? I should have numbered the pages. But this is a table adapted from that article, Mariani and Venuti, that compares and contrasts and puts into context what I just said and serves as a basis of my opinion of the concept that it's apples and oranges, that immune response to HPV is not equivalent. Immune response to HPV infection is not equivalent to an immune response to HPV vaccine.

So to go through them, and hopefully quickly

because I think it's pretty straightforward, is that in an HPV infection there's no virus inducted cytolysis or necrosis, meaning that the virus hides out intracellularly and doesn't cause lysis of cells and liberate the damage associated products, the DAMPs, or pattern recognition molecules that have been attributed to activating the innate immune system.

THE COURT: Ms. O'Dell, pending more testimony from Dr. Rose, I understand the basic point that the immune response to Gardasil is not the same as the immune response to an HPV infection. So there's a lot of details, but I understand that general point.

So unless we hear from Dr. Rose some dispute about that point perhaps we can move on to the next because I understand the big picture. If Dr. Rose is okay with it, we'll hear from Dr. Rose about that. Unless there's some dispute about the details, we can probably move along.

MS. O'DELL: Okay. That would be fine, Your Honor. I would just note for the record the Mariani paper is Exhibit 18. It's been put in the record previously.

BY MS. O'DELL:

Q So with that understanding regarding the

innate immune response to the virus versus the vaccine, Dr. McCabe, transition to the specific cause and effect in this case. And what methodology did you use to develop your opinion as to specific causation?

A Well, one thing I think that's helpful just as a rubric is the Bradford Hill criteria for causation. So I followed Bradford Hill.

Sir Bradford Hill was an epidemiologist who I think back in the '60s -- this rubric is attributable to his work and followed by scientists who are interested in understanding what the method for establishing or vetting causation of diseases, initially cancer by Bradford Hill, but then can be broadened to consider other diseases.

Q Okay. Now if you would walk through for us, please, the criteria and how you applied the criteria to the specific facts of this case?

A Sure. So the simplest one to understand is temporal sequence. And I think everybody agrees that if there wasn't a temporal sequence, meaning there was some exposure to in this case Gardasil or an environmental agent prior to the manifestation and presentation of the disease, that we wouldn't be here. So temporal sequence is certainly important and a good starting place.

Biological plausibility. And I skip around a little bit, but biological plausibility in my mind is a mechanism of action. Are there studies and application of this criteria? My analysis here is are there studies that show that there is a or are logical mechanisms of action that could lead to the end point that's being studied.

Another example of the criteria is strength of association, which is also linked to consistency and unbiasedness of findings. These are criteria that really go to epidemiological studies. So the question in my analysis is are there epidemiological studies that link Gardasil to autoimmune diseases in general in human population studies or to specific juvenile idiopathic arthritis specifically.

Biological gradient is an important criterion, and in a biological gradient dose response, a fundamental principle of toxicology, but also applicable to immunology. The dose response and the dose here is of relevance again in considering the difference between the immune response to vaccine versus the immune response to natural infection, doses and time scheduling of the vaccine and things of that nature, so a criterion that is under consideration.

You know, experimental evidence is basically

what's the published literature or data obtained by other methods that are valid and have been peer-reviewed, and reasoning by analogy in this case would be well, what do we know or what can we say about other vaccines or other environmental triggers, infections, and how does that inform us to how environmental triggers can cause systemic juvenile idiopathic arthritis and specifically Vanessia's disease.

Q How does the 2005 Pinto article you cite in your report -- I believe it was Exhibit 26 -- inform your opinion in regard to your analysis?

A So, yes. We're going to Pinto 2006. 2005.

Q 2005.

A And this is Exhibit No.?

Q 26.

A 26. And it's Slide No.?

Q 12.

A 12. And again, this is just the cover page of that particular article. This is a --

MS. O'DELL: Excuse me, Dr. McCabe.

THE WITNESS: Sorry.

MS. O'DELL: Just for purposes of the record, Your Honor, we changed the order by a couple of slides. This is actually for purposes of the

record Exhibit 38/16 and 17.

BY MS. O'DELL:

Q Sorry. Please proceed, Dr. McCabe.

A I view this to be an important paper in vaccinology, the study of vaccines, and Pinto, the authors, as much state that in the article in that this is the first paper that employed the power of multiplex cytokine analysis to the response of a vaccine in human beings.

So it's a technical tour de force. For most of my career scientists or immunologists were used to looking at single cytokines and doing single cytokine analysis one after another, but this is an assay that's able to look at multiple cytokines from small samples, so from limited serum obtained by the subjects that are part of this study. So this is a study that compares the cytokine response, measuring multiple cytokines, found in individuals who have been vaccinated with an HPV-16 L-1 vaccine. So it's not Gardasil, but it contains one of the L-1 proteins present in Gardasil.

So it's a research study geared towards studying the cytokine response, and the experimental design I think is very good and is very appropriate in that, if we can go to the next slide, which will be

Slide 13. And here I lifted Table 1 from the paper to make some important points, but let's first talk about the experimental design.

So this is an experimental design where individuals have been either vaccinated with HPV-16 or not. Those not were given a placebo. And there's a comparison between those who were vaccinated and those who were not in several columns. It's an ex vivo analysis of their cytokine production. What I mean by ex vivo, as opposed to strictly in vitro.

The individuals, the subjects in this study, were immunized in vivo, that is treated in vivo, with vaccine. This is a standard way in the laboratory, in a research laboratory, to assess their cytokine response. It's analogous to doing a diagnostic assay at that level. It's analogous to doing a diagnostic assay to measure their C-reactive protein levels or acute phase response.

There's two parts of this. There's two parts of this publication to talk about. This is the table on whole blood analysis. There's another table on peripheral blood mononuclear cells. I pulled the table out on whole blood analysis because the whole blood analysis also represents a technological advance, the ability to measure biological modulators,

the ability specifically here to be able to measure cytokines produced in a whole blood assay as opposed to introducing the variable of separating out peripheral blood mononuclear cells from the rest of the cells in blood.

So prior to this technological advance the other constituents of whole blood would interfere with assays, and that problem has been solved, and it's useful now because when one isolates peripheral blood mononuclear cells, which I have done many times in my research career when I was tinking, one loses certain cell populations and particularly the cells of the innate immune response. So I think it's more appropriate to focus on the whole blood assays perhaps.

So that's the experimental design. The experimental design is assess cytokines in a whole blood assay ex vivo and to build in a dose response to the in vitro part that provokes changes in the cytokines. Time is also built into the experimental design, and it's an appropriate time interval in that cytokines are being measured at time zero, either at the time of vaccination or shortly thereafter, but at a time where you wouldn't expect a change, a vaccine elicited change in cytokines, and then at two months

and seven months postvaccination.

And as I said, it's a technical tour de force. It's a data tour de force. There's a lot of data here. And the take-home message to this is in part what you'd expect, but it was important in my methodology to find papers like these. The expectation is that there's been a lot of research on the immune response to Gardasil at the level of antibody responses.

That's what the production of the vaccine is really mostly about is to produce high levels of antibodies from B cells that would be specific for the four components of the vaccine, the four L-1 proteins that make up the vaccine, and would afford immunological protection by the effector mechanisms that I spoke about. For example, neutralization and inhibition of upon challenge with an infection, HPV infection, of the virus being able to effect, get into cells.

There's been less work on cytokines, but nevertheless some, and this is an important paper in that context that shows what I would expect based on what I've told you earlier about how the immune system works and the different mechanisms at play in adaptive immunity and innate immunity to drive that antibody

response.

And in this case cytokines of both the adaptive immune system and the innate immune system are elevated in the vaccinated population, so TNF alpha is increased, interleukin-6 and interleukin-1 beta as a form of interleukin-1. The data demonstrate that there's a dose response, that in comparing response to the L-1 presence as a challenge or stimulator in vitro such as an elevated response over the vaccine, the absence of the challenge in vitro, demonstrates that there's an elevation of cytokines derived from T cells, such as interleukin-2, interferon gamma, interleukin-4, interleukin-5.

And as I mentioned, in part this is what you expect, that for this to be a strong vaccine you'd expect cross-talk between the innate immune system and the adaptive immune system. You'd expect it to be at the level of cytokines.

THE COURT: Can you show me what demonstrates a dose/response relationship?

THE WITNESS: Yeah. Sure. So the interleukin-2. So if you look almost all the way over to the right column, L-1 at One Micrograms, if you just focus on interleukin-2, for example, that the L-1 at one microgram at seven weeks, the level is 16, but

at the same time at a dose of 10 the level is 130. So more stimulus in vitro, more cytokine produced. And there's a couple of examples that you see with TNF alpha as well following the same. You see it with interleukin-4.

THE COURT: But it seems like it doesn't happen with all.

THE WITNESS: It doesn't happen with all, and that is the inconsistency in the assay. You can get mired down a little bit too much in the details here, but the big picture, take-home message is that there's a lot of cytokines that are being elicited by immunization.

One thing just to be fair so that there's no misrepresentation here is that I cut this table off, I believe, for the PHA. There's a mitogen. That's just basically a positive control. That's part of the table that I don't have here because -- it's a good internal control for it to be in the assay, but --

THE COURT: We should look at TNF alpha, right? I think it's your testimony that TNF alpha is one of the cytokines that contribute to the onset of systemic JIA.

THE WITNESS: Sure. And in the context of this case it's also the cytokine that's targeted for

Vanessia Koehn's therapy.

THE COURT: So is this showing that a Gardasil-like vaccine triggers an increase in TNF alpha specifically?

THE WITNESS: It depends on what you meant by specifically. It's not showing an increase if by specifically you meant exclusively, no.

THE COURT: We have like a dozen cytokines listed. But for the TNF alpha cytokine does this show an increase after you receive the Gardasil-like vaccine compared to the placebo?

THE WITNESS: Yes, it does.

BY MS. O'DELL:

Q Dr. McCabe, why don't you walk us through the table and the specific findings?

A Let me make sure I have --

MS. O'DELL: And, Your Honor, for purposes of the record the Pinto article is Exhibit 26 at page 4 is where the table is located that appears on this slide.

THE WITNESS: Sure. So let's focus on TNF alpha, and I've placed a -- I wonder if I could -- I probably can't do it here. I've segregated out the time zero time point going across the table just to orient us. And so in an experimental design this is

what we mean by negative controls. So at time zero you see going across the table if you just compare, for example, the vaccine group, and let's just -- that would be more appropriate. Let's look at mean values.

So each bundle of information of Vaccine Versus Placebo under Media and then Vaccine Plus Placebo under L-1, 10 Micrograms, and then Vaccine Plus Placebo under One Microgram. Each bundle of information contains the data from the vaccine group and the placebo group. And at time zero, as you would expect, without any immunogen in vitro you establish a baseline level of TNF alpha that can be produced in that assay, which is 3.6, 3.8. I'm sorry. I'm just going to focus on means, which is 3.8 and 2.9 in the in vitro portion of the experiment.

Again, this is at time zero so there's not much of a difference, but there is an increase because this is the first challenge in the in vitro portion with the immunogen so there is an increase in the levels of cytokine relative to the first columns and also at the lower dose and not much of a dose response there, as you'd expect.

Now you go to two months postimmunization and again focusing on the TNF, the mean in the nonvaccinated population, 3.2. It's statistically not

different from the 3.8 at zero, and that's with -- I'm sorry. That's with the media response in the vaccinated group.

THE COURT: What does media mean there?

THE WITNESS: So media is zero, zero L-1. So you can think of media -- so this is an in vitro assay occurring in tissue culture media, and you can think of media as L-1 zero. Does that help?

THE COURT: Well, isn't that the same thing as a placebo? Like why would that --

THE WITNESS: No. Okay. The placebo is the in vivo portion of this experiment. The placebo is the control for the vaccinated population.

THE COURT: The placebo group doesn't get any vaccination.

THE WITNESS: Correct. They're treated with a placebo. I mean, the best way to have a placebo, and I don't remember the details here, is to do everything to those patients that you do to the vaccinated group short of supplying them with the target immunogen, the vaccine, the HPV-16 L-1 protein.

THE COURT: So in like the third column where it says Media Vaccine --

THE WITNESS: Uh-huh.

THE COURT: -- are you saying that that's

like L-1, zero micrograms?

THE WITNESS: Correct. In the assay.

THE COURT: Okay.

THE WITNESS: So these were people who were vaccinated with HPV-11, their blood was analyzed at time zero, at time two months and at time seven months and then put in this assay to determine what cytokines are being produced as a function of the immunization --

THE COURT: Okay.

THE WITNESS: -- as well as what's the frequency of cells that exist in those populations as a consequence of immunization. And by frequency of cells, that are producing these specific cytokines.

THE COURT: So then for TNF alpha, let me go over a half dozen columns. We have like the L-1, 10 Micrograms. There is more TNF alpha at seven months than there was at two months.

THE WITNESS: Correct. So there's a time component to the response, as well as a dose response.

THE COURT: There's a bigger jump from zero to two months than there is from two months to seven months.

THE WITNESS: And actually I think that does fit, and I don't want to -- I'm going to make the

statement, and then I'll qualify it. In the studies on Gardasil zero conversion, some of which I have figures for later on, most of the immune response in terms of the antibody response and the antibody titer increasing and then plateauing is occurring in that zero to two month window of time and not so much in the two to seven month period of time.

Now, the qualification of that is that's a little bit of an apples and orange comparison because that's with Gardasil and this is with the baculovirus system in this specific instance with the HPV-16. But, yes, there is more of a jump, but nevertheless a jump, and I think that's the point is that these are data that represent that there are increases in these types of cytokines within the timeframe of the immunization.

And I think there's a general take-home message here that these documentation that as expected, given the strong immune response driven by the vaccine, that there would be cytokines that are produced at higher levels, and indeed they are as exhibited and illustrated in this particular paper and others, and that it's applicable to the argument that's being made in the context of Vanessia Koehn's generation of her disease, given the commonality in

the cytokines in SJIA.

BY MS. O'DELL:

Q Dr. McCabe, what cytokines specifically are implicated in the development of SJIA?

A Well, I think I said that earlier. Interleukin-1, interleukin-6, TNF alpha and interleukin-18. But others as well, but those are the most -- those are the proinflammatory cytokines for which the most information exists at this time.

Q And as to TNF alpha, IL-6 and IL-1 beta, does this table show that there was an increase in those cytokine levels after vaccination?

A Yes, it does. The other thing is -- the answer is yes, it does, and the other thing to bring out in the appropriateness of this experimental design is that there is statistical tests that were done showing that these are statistically increased levels. And that's what the P column stands for. Anything with a number after it is showing statistical significance.

So just by doing it that way is that you look down the column, the first pair of columns in looking at vaccine versus placebo in the media group and looking at the P value table it's NS everywhere, meaning it's not specific. And then looking down the

next pair you see again vaccine versus placebo, and in the vaccine group at 10 micrograms stimulus in vitro you see which cytokines are viewed to be statistically increased over the placebo control, the appropriate control in that comparison, and many, if not all, of these cytokines are being elevated, and the same or similar story in the L-1, at the L-1 dose.

THE COURT: How does IL-1 beta relate to interleukin-1?

THE WITNESS: Most of the time when you talk about interleukin-1, most of the time when you're reading about interleukin-1 it means interleukin-1 beta. Interleukin-1 comes in two isoforms, beta and alpha, and beta is the most prominent form and the one that everybody is considering. So it's the same thing.

THE COURT: Okay.

BY MS. O'DELL:

Q And was there another Pinto article that you relied upon? Well, let me ask you first. Is there anything else about this Exhibit 26, the Pinto, the 2005 Pinto publication, we've not covered?

A There is. Give me a --

(Pause.)

A Well, as I mentioned to you I just pulled

out the whole blood data for this, but there was also work done with peripheral blood mononuclear cells.

You know, Dr. Rose, to be frank, doesn't share the same enthusiasm as I interpret his report for this study that I do. And one of the things that I wanted to discuss in that light was his comments about the data on interleukin-8 in his report, and that's on page 7 of his report. If there's an exhibit number, is it Exhibit A?

Q It is Respondent's Exhibit -- excuse me just a moment. Let me get that. It's Respondent's Exhibit A. Sorry.

A It's not entirely clear, his portion of the report with respect to this, but he'll have his chance perhaps to clarify, but I have some things I wanted to address there.

(Pause.)

A So a couple different levels that I'll address in this. First, he's made a statement about some interesting findings in the context of Vanessia's disease is, for example, the data on interleukin-8, a relevant cytokine in systemic JIA, and he cites Reference 3 of his report. Reference 3 of his report is Verstraeten, and Verstraeten doesn't discuss interleukin-8 as far as I could tell. I think he

means Reference 2 of his report, which is Mellins, and Mellins doesn't discuss interleukin-8 either as best I could tell. It discusses interleukin-18. That is more than a typo.

So interleukin-8, which is a chemokine, the chief function is to drive leukocyte movement across tissues, particularly neutrophils or granulocytes. There's reasons why interleukin-8 and neutrophil trafficking would be involved in the neutrophil elevation component of SJIA, but that's not what these studies are addressing. So interleukin-8 is not as relevant a cytokine in systemic JIA and certainly not discussed in the Mellins report.

The other level of this and just try to understand is that he's talking about a cytokine that's not relevant to the disease, and even if it was interleukin-18 stating that it would be interesting if it had changed and yet the interleukins and cytokines -- IL-6, TNF alpha, interleukin-1 -- that are changing as a consequence of vaccination in the Pinto paper, that's not interesting to him.

That was puzzling to me in his overall opinion. It's interesting that those cytokines -- that cytokine, interleukin-8 -- which isn't changing, he seems to be saying there that it would be

interesting in the context of her disease if it had been changing and then it's the wrong cytokine.

So then the last part of this is that there's no basis of the comparison between the Pinto article and the Mellins article if we're talking in Pinto IL-8 or Pinto is providing data about interleukin-8 and the Mellins article is talking about the importance of interleukin-18, which is a proinflammatory cytokine member of the interleukin-1 family in the pathogenesis of systemic JIA.

Q Okay. So to the degree that Dr. Rose has referenced interleukin-8 in his report, that reference is in error?

A As I understand what he's saying here in his report, yes.

Q Okay. So now having worked through that, was the Pinto article I think we referenced as Exhibit 28, did it also inform your cause and effect analysis?

A Yes, it is. And as I said at the beginning, I think this is a very important paper, and in my methodology and in considering the issues that are relevant in this case this was part of the biological plausibility mechanism of action piece of my analysis.

Q Yes. And specifically if you would take us through that paper? Let me ask just to make sure

we're on the same page, Dr. McCabe. I'm talking about the 2007 Pinto article.

A Sure. Pinto is the senior author on that paper. It's an article. The first author is Garcia-Pineres. Garcia-Pineres, P-I-N-E-R-E-S.

And this is the same lab, but in thinking about what my methodology was and is there a consistency of findings. You know, it's great to find one paper that supports an analysis, but I'm more satisfied as a scientist if I can start building a consensus from other papers in the literature.

So this is again another analysis of cytokines. This is page 14 of the PowerPoint, which just is again sort of the method to my madness, which we should be seeing repeated here as I put the cover page in of the article that I'm talking about, which is Cytokine and Chemokine Profiles Following Vaccination With HPV Type 16. So this again is a baculovirus system, and there's --

THE COURT: Ms. O'Dell, I think just for the record you can keep Exhibit 38 running.

THE WITNESS: Yes. Exhibit 38. Sure.

MS. O'DELL: Yes.

THE COURT: It's 18 and 19? Page 18 and 19 for Exhibit 38?

MS. O'DELL: Yes, sir. That's correct. And the underlying article is Exhibit 28.

THE WITNESS: And the take-home message to this paper is depicted in the next page, which is page 15.

MS. O'DELL: I'm sorry, Dr. McCabe. It's Exhibit 38, page 19.

THE WITNESS: Okay. I lost track of page numbers here. So you're telling me this is 19 now?

MS. O'DELL: That's right.

THE WITNESS: Thank you.

MS. O'DELL: I'll note the page number. You just tell us about it.

THE WITNESS: Sure. And again, I'm cutting to the chase on this in that this is again an analysis of the cytokines and chemokines, interleukin-8 being a chemokine, MIP-1 alpha, that you see at the bottom of this figure, another chemokine, for example. You know, conceptually there's not much to really get bogged down in in thinking about cytokines and chemokines. Chemokines are a subset of cytokines that facilitate cellular trafficking and movement within the body within an immune response.

So the take-home message here is that this is yet another study that shows that a vaccine like

Gardasil can elicit changes in proinflammatory cytokines, as well as adaptive cytokines. The data are displayed via this two-dimensional cluster analysis, which is really a way using a color pattern paradigm, red meaning increases, green meaning no increase or, sorry, green meaning a decrease. Red meaning an increase, green meaning a decrease, black meaning no increase.

And at the top you see that there's a number of subjects, so you see the tree at the top, a number of different subjects and then letters V, V across and then P, so that's vaccine versus placebo, I believe. And comparing the cytokine responses and the increases in these, again multiple cytokines both proinflammatory, IL-1, interleukin-6. Here it's IL-1 alpha that they're measuring, so both forms of IL-1. IL-1 alpha, TNF alpha, interleukin-6, as well as cytokines that comprise the adaptive immune response.

That in many of the subjects, who fall under this Cluster 1 on the left-hand side, behave the same way. Everything's red, and there's an increase in many cytokines. And then there's a second group of subjects in Cluster 2 who have increases, but not as much as the subjects in the others, and then there's a smaller group of subjects, Cluster 3, that actually

have some decreases.

So it's an honest and valid and powerful way of depicting the data, which the message being is that there is variability in response, that different subjects, because they're humans and there's genetic differences and this isn't a -- by humans I mean this isn't an animal study where there's genetic homogeneity.

These are humans that have different lifestyle factors, different environmental triggers, different immunological backgrounds, different immunological histories, different genetic backgrounds, are going to respond differently if you address this in a detailed way, but the big picture, 30,000-foot view is lots of changes elicited by the cytokines, by the vaccine in cytokines.

BY MS. O'DELL:

Q And in addition to the two Pinto papers that we've referenced, are there additional scientific articles that support this conclusion that there's an upregulation of cytokines in the --

A Yes.

Q -- of Gardasil or one of the component vaccines?

A There are. They're mentioned. They're

referenced. They're discussed in my report and mentioned in my report. So a few things about that. So, yes. The answer is yes, there are.

I talked about the two papers from the Pinto lab because those are the papers that are most technologically advanced as I viewed them, were most comprehensive in the cytokines that were analyzed and papers that demonstrated that there's an increase in proinflammatory cytokines that are relevant to systemic juvenile idiopathic arthritis.

There are additional papers that I have cited, one of which is Evans, which is Exhibit 30. And I think a couple points to make here, just general points, is that in my methodology, again thinking back to Bradford Hill criteria, is there consistency? Is there reason by analogy and by reason analogy here? So by consistency I mean are there multiple papers, multiple papers that have been peer-reviewed that support the hypothesis?

And by reason by analogy, the two papers that I've talked to you about so far were a vaccine that's somewhat similar to Gardasil, but is based on HPV L-1/16. The Evans paper uses HPV-11. Experimental design is comparable in making a comparison between vaccinated and not vaccinated.

Looking at other markers of immune function and showing that there is an increase in lymphoproliferation, that's one of those words that immunologists make up, so let's break it down. Lympho meaning lymphocytes. Proliferation meaning cell growth, which is part of the adaptive immune response that T cells responding to HPV-11 L-1 are going to expand.

And that could be measured and oftentimes is and in the Evans paper was measured in the context of HPV-11 immunization again in an ex vivo type paradigm, which is standard for these types of assays, according to a schedule of the vaccine.

And this paper shows that in individuals with high levels of neutralizing HPV antibodies there's a peak and a plateau, six weeks, and you'd expect that in order to achieve that high level of antibody that it would require T cell help. T cell help would manifest as increases in T cell proliferation and upregulation of certain cytokines, here less comprehensive in the cytokine analysis in that they focused on adaptive cytokines, cytokines that are more attributable to the adaptive immune response, interferon gamma and interleukin-5.

There's another study by Emeny, which is

Exhibit No.?

Q 32.

A 32. And this is a paper that again documented increased lymphoproliferation, as well as increased cytokine levels after immunization, and I believe that was -- again, it was more limited in scope than the Pinto paper, but measured interleukin-2, interleukin-5 and gamma interferon and showed changes in those, showed increases in those cytokines as a function of immunization.

Q Any others that support the upregulation?

A Let met see.

(Pause.)

A I think that's it.

Q Okay. Great. So putting in context these papers in regard to the upregulation of cytokines, the proinflammatory cytokines and the effect elicited by Gardasil or Gardasil-like vaccines, what is the cause and effect relationship? If you can summarize that for the Court, please.

A The central element of Vanessia Koehn's disease that establishes a cause/effect relationship in my opinion is the proinflammatory cytokine profile that is shared by Gardasil vaccination and the pathogenicity of systemic juvenile idiopathic

arthritis.

This cause/effect relationship is supported by the scientific and medical literature that implicates proinflammatory cytokines and inflammatory responses and innate immunity in the pathogenesis of systemic juvenile idiopathic arthritis. It's supported by the scientific and medical literature that demonstrates that HPV vaccine is a strong and potent immunogen that stimulates the production of these same proinflammatory cytokines, as well as adaptive and innate immune responses normally attributable to protective immunity.

Thirdly, this cause/effect relationship is supported by Vanessia Koehn's medical records, so although no direct testing of cytokines were done or would be expected to have been done, her clinical presentation -- fever, rash, joint pain -- is consistent with increases in proinflammatory cytokines, namely interleukin-1, TNF alpha, interleukin-18 and IL-6, and diagnostic tests -- increases in acute phase proteins, C-reactive protein, elevation of sed rate, increases in neutrophils, increases in platelets -- are consistent with proinflammatory activities.

Finally, the use of and the efficacy of

therapeutic agents to treat Vanessia Koehn's disease support a role for proinflammatory cytokines in her disease course.

Q And what specific treatment are you referring to?

A Well, all of them, but start with -- I mean, you asked me which specific treatments, and that's a good way of framing the question because the most specific would be Enbrel because it's a specific treatment targeted at TNF alpha, but Methotrexate is a drug that is targeted at proinflammatory cytokines. Methotrexate is a drug that is targeted at inflammatory processes, including proinflammatory cytokines.

Prednisone, corticosteroids function by increasing -- sorry, by decreasing cytokine production in disease, but Prednisone is nowhere near the specificity that Enbrel or any of the other specific inhibitors of cytokines, proinflammatory cytokines that exist, such as Anakinra for interleukin-1 or -- I can never remember how to say this -- Tocilizumab.

DR. ROSE: Tocilizumab.

THE WITNESS: Thank you, sir.

DR. ROSE: Tocilizumab.

THE WITNESS: Tocilizumab, an antibody to

interleukin-6 that's used as a therapy much more specific to that particular cytokine, targets that specific cytokine and is much more specific than a corticosteroid. So all of them and in that order.

Naproxen is an anti-inflammatory agent either directly targeting the cytokines or the activities elicited by those cytokines.

BY MS. O'DELL:

Q And focusing on Vanessia or continuing to focus on Vanessia for a moment, after she received Gardasil Shot No. 3 what was her condition? Explain to us the relevance of her condition at that time.

A I'll answer it this way. One way of testing a hypothesis that an environmental trigger causes an autoimmune or an autoinflammatory disease would be to focus on individuals that already have the disease, in some ways because of power, lack of power in some of the other epidemiology studies that can be conducted for rare diseases like SJIA. That's a valid approach.

So the experiment is to look and see, investigate in individuals who have the disease when they're given a trigger, whether it be an infection or some environmental agent or some vaccine, whether it exacerbates the disease, whether it causes any change not in the development of the disease because the

disease is already developed by virtue of them having diagnosed with it, but does it cause any change in the progression of the disease.

So on one level that's an appealing design of an experiment or way to test. The downside of it is it has some complications because here we have, and I think it has some relevancy issues here because here we have an individual who is receiving therapies, anti-inflammatory therapies, at the same time that she's receiving that third dose of Gardasil.

So the data, it's difficult also given that we have one there, one individual. It's difficult to take too much away from it. If there were no changes, part of that would be I would suspect or wonder and consider whether well, the reason that there's no change is because at the same time that a stimulus is given an inhibitor is present. So that's one issue, and I think it's relevant.

The other issue, and my read of the records is it's not necessarily clear. It's not necessarily true that she didn't have a flare after that third shot. She had the third shot on August 19, 2008. August 27, so almost a week later, she was described as having a rash that she hadn't had for quite a while. She was having an increase in her joint pain

in several joints.

And so whether or not it's an exacerbation due to that particular immunization or not, again it's difficult to say for the same reason that it's difficult to say one way or another because of the presence of the inhibitor at the same time. Too many variables. You know, one thing scientists don't do is change too many variables.

THE COURT: Ms. O'Dell, do you happen to have a cite for the August 27 visit handy?

MS. O'DELL: Yes, Your Honor, I do. I believe it's at Exhibit 8, and the page number on that is -- excuse me, Your Honor. Let me pull it out really quickly. It's Exhibit 8, page 48 through 50.

MR. WISHARD: You're referring to the physical therapy?

MS. O'DELL: Correct.

THE COURT: Thank you.

BY MS. O'DELL:

Q Dr. McCabe, let's turn our attention very quickly actually to temporal association between Vanessia's vaccination with Gardasil to her onset of symptoms. Please outline for the Court your opinion in regard to temporal association.

A So this is page 20?

Q This is page 13 of Exhibit 38. This is -- in question.

A Okay. Again, to make this flow the take-home message and the concept that informs my opinion in this is that the expected interval between vaccination, Vanessia's vaccination with Gardasil, and the onset of the autoinflammatory disease is predicted by the time period that measurable changes in the immune response are known to be elicited by the vaccine.

So the schedule of the vaccine and these references that I'm citing here, as well as in my report, show at the level of the antibody level where again most of the work is being done that within that zero to two month time period there's a very potent immunogen has been offered and a very strong humoral immune response has been elicited. And think back to my slide on innate and adaptive immune mechanisms controlling those responses that all that business, all of those immune mechanisms are occurring during that time period and then with each successive booster shot to drive that potent immune response.

Q Have you prepared a slide that will help the Court?

A Yes. The next slide, which is Slide 21,

which is one of the slides coming from --

MS. O'DELL: Your Honor, just for the record, the slide that we're referring to is Exhibit 38, page 14.

THE WITNESS: This is taken from Frazer. And is this Exhibit 25?

MS. O'DELL: Exhibit 25.

THE WITNESS: And this is one of many papers that I cited and I think show consistently that with respect to HPV-6 immunogenicity, -11, -16 and -18, all of which are components of the vaccine, that the steep portion of the curve in terms of measuring the immune response and quantifying the immune response in these individuals occur during this timeframe of immunization.

The Pinto article that I discussed on cytokines is also supportive of that and perhaps more supportive at the level of proinflammatory cytokines since that's what's being measured in that article, that during that timeframe between zero and two months that there's a strong cytokine response occurring.

So there's the general concept of temporal association, that the disease emerged manifest in June of 2008 in a time period postvaccination and at a time period that I expect these immunological events to be

occurring.

Q Okay. Dr. McCabe, tell us. You cited the Chao article or you put in the record the Chao article. And please walk us through the significance of the Chao citation in Exhibit 34.

A Yes.

MR. WISHARD: You said Exhibit 34. I think it's 43. Is that correct?

MS. O'DELL: The Chao article is actually Exhibit 34.

MR. WISHARD: Oh, I'm sorry. You're right. My apologies.

THE WITNESS: Chao was a paper that was published or at least I became aware of after I submitted my supplemental report last fall. It's significant and it's important again in the context of the methodology that was used and in following Bradford Hill criteria.

One of the Bradford Hill criteria is consideration of strength of association, which gets at epidemiological studies, and the hypothesis to be made there or the concept, the test, is are there epidemiological studies that support the development of systemic JIA in human populations immunized with Gardasil. And there aren't any. Really the message

is that there aren't any.

So Chao I became aware of. So this is a large -- by large meaning many, many subjects -- human subjects epidemiological study. It comes from the Kaiser Permanente Southern California patient group. So there's a couple of things here to talk about is that within -- I'll do it again. In the context of Bradford Hill, one of those criteria was to ensure that there's no biasedness of findings.

Some things I've read in the literature and I think some scientists have an opinion that the epidemiological studies that have been supported by the manufacturers are questionable because they may be biased. I don't necessarily hold that opinion, but the issue of bias is relevant.

This study, as part of the design and the execution of the study, included a safety review committee, so it just wasn't some individual epidemiologist or single epidemiologist who was conducting the study. They integrated scientific oversight. That's what peer review is all about.

That's what scientists like myself who serve on editorial boards or serve in study sections as I talked about earlier, that's the scientific process. That's the peer review process. And that peer review

process and oversight is built into this study. And that's just great.

So it's a safety review committee, and they're charged with reviewing the safety data and reviewing the study and the results and the data and comprised of five experts external to the investigation team, so that goes in my mind and speaks to biasedness and unbiasedness. It included a general pediatrician, a clinical epidemiologist, a perinatologist/teratologist, a vaccinologist, a pediatric rheumatologist and a pharmacoepidemiologist. I said five. I think I may have counted six people. At least one of those people must have had two hats.

So this was a safety review committee, and what I think is relevant here and the reason why I lifted this figure out of the paper is that this study, which has this scientific oversight built into it, considers the risk period for developing autoimmune diseases or autoinflammatory conditions in people immunized with Gardasil -- that's what the HPV-4 there is, and the arrows going down obviously are the schedule for the vaccine -- and the risk periods for analysis. So that's supporting my opinion that the relevant immunological events that are occurring postvaccination are occurring during the

time period that I suggested.

The other reason for including Chao and for discussing it again is in the overall methodology that I followed and an example of that. I'm not biased in my opinion I don't think in acknowledging that it would be helpful to address the connection between Gardasil vaccination and systemic juvenile idiopathic arthritis if there was epidemiological studies that supported it, but we don't have them. That means in my opinion we rely on other criteria within Bradford Hill and other methodology to get there, such as I've stated.

This is a paper that had some 189,000 individuals. That seems like a lot. It didn't study systemic JIA as best I can tell, and I think this is part of the problem here. And what I mean by problem, part of the problem in understanding the absence of epidemiological studies in that this is a disease, as I understand it, that has an incidence of between two and 20 per 100,000. Two and 20 per 100,000.

So it's a rare disease. Even at 189,000 subjects, you'd expect three or 30, depending on between two and -- sorry. Yeah. Between two and 20. Somewhere between three and four on the lower end of that and 30 and 40. My view and what I've read and

what I understand is that the incidence is more towards the lower end, and indeed in this paper there's no specificity in the analysis of SJIA, and I suspect that that's because there's too low an incidence of the disease. It's too rare a disease to do that type of an epidemiological study or to expect to get meaningful statistically relevant and valid results from.

So what do you do about that? You, as I said, consider other elements of Bradford Hill or you adopt experimental designs such as I mentioned before and study exacerbation in individuals who have already been diagnosed and have the disease.

BY MS. O'DELL:

Q Okay. And so in sum, to the degree that there was no test -- well, let me say this. In sum, in order to adequately test for SJIA in subjects who've been vaccinated with Gardasil, there would need to be a much larger sample size. Did I understand your testimony correctly?

A Yes. Yes, you understand my testimony to that extent. Whether it's important for this, but that would be a burdensome, cumbersome study to do, and I'm not advocating or suggesting that that's something that the manufacturers of the vaccine should

have to do in my mind.

Dr. Rose makes a statement in his report that there aren't any epidemiological studies, and he doesn't expect there will be any. You know, in fairness to him he has a different -- as I understand his report has a different reason for thinking that, but I agree with him on that aspect of it. There won't be any because they would be difficult to do and difficult to interpret the data.

Q And is that view shared by Prakken and others?

A Yes. So in the next slide -- I lifted this out of Prakken because it concludes --

MS. O'DELL: For the record, Your Honor, it's Exhibit 12.

THE WITNESS: This is a paragraph lifted out of Prakken, and I talked about Prakken earlier in that cartoon. Prakken has a discussion of environmental triggers and environmental factors in the disease, so this is a paragraph that's lifted out of page 2141 under Environmental Triggers.

Really the take-home message to it or one important -- there's a couple of important things here. One important thing is the last sentence which essentially is what I just said, which starts with,

"Again, much larger studies, including both genetic susceptibility and up-to-date immunological analysis, will be needed to define the role of environmental triggers in JIA."

You know, that's true. I think the data, the science is moving in that direction by virtue of some of the approaches that you see in the Pinto articles that I cited that there are analysis of cytokines and proinflammatory cytokines. That could be done in the context of the vaccination scheme. You know, much larger sample sizes in any of these epidemiological studies.

And also Prakken, in this section of his review, illustrates the general concept that infections and vaccines have been suggested and vetted by scientists and clinicians in the cause of these types of diseases, and by and large the outcomes have not been particularly fruitful. And again, that's probably for other reasons that I just discussed.

BY MS. O'DELL:

Q Dr. McCabe, based on your testimony today regarding general causation and cause and effect of Gardasil and the development of SJIA, have you formed an opinion about causation in this case?

A Yes, I have.

Q And do you hold that opinion to a reasonable degree of scientific certainty?

A Yes, I do.

Q And if you would outline for the Court your opinions in this case.

A Three general elements. Number one, that Gardasil elicits the production of proinflammatory cytokines that have been strongly implicated in the development and progression of systemic juvenile idiopathic arthritis.

Two, there's an obvious temporal association between Vanessia Koehn's vaccination with Gardasil and her symptoms and diagnosis with systemic JIA. The interval of time between her vaccinations and onset of symptoms of autoinflammatory disease is predictable by the time period when immune response are seen by the vaccine.

Third, Vanessia Koehn's vaccination with Gardasil was a substantial contributing cause of her development and progression of systemic JIA as evidenced by her medical records, which document clinical markers and clinical presentation indicative of elevated proinflammatory cytokines, as well as the scientific medical literature that supports a conclusion that connects Gardasil and systemic JIA by

a common element, a common mediator of the disease process, namely proinflammatory cytokines, and this is supported by her clinical improvement upon receiving therapies that target the activity levels of these same proinflammatory cytokines -- Enbrel, Methotrexate, Naproxen and other anti-inflammatory drugs, including Prednisone.

Q Okay. And in terms of her vaccination with two shots, Shot 1 and Shot 2, of Gardasil, but for those two vaccinations would she have developed medical problems, specifically systemic JIA, in June of 2008?

A In my opinion, no, she would not.

Q Do you hold that opinion to a reasonable degree of scientific certainty?

A Yes, I do.

MS. O'DELL: Your Honor, I don't believe I have any further questions at this point.

THE COURT: Why don't we go off the record for a moment?

(Whereupon, at 12:50 p.m., the hearing in the above-entitled matter was recessed, to reconvene at 1:30 p.m. this same day, Thursday, June 21, 2012.)

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AFTERNOON SESSION

(1:29 p.m.)

THE COURT: Let's go back on the record. After lunch, Mr. Wishard, do you have a few questions?

MR. WISHARD: I do. Thank you.

Whereupon,

MICHAEL J. McCABE, JR.

having been previously duly sworn, was recalled as a witness herein and was examined and testified further as follows:

CROSS-EXAMINATION

BY MR. WISHARD:

Q Hi, Dr. McCabe.

A Hello.

Q Just to highlight a few basic points before I go into things too deep. No dispute at all that Vanessia has systemic JIA?

A Correct.

Q And the term systemic juvenile idiopathic arthritis. The term idiopathic means I think generally unknown cause or cause unknown, correct?

A It can mean that, and that's one interpretation of idiopathic. Another interpretation of idiopathic is multiple causes or multiple contributing factors.

Q And in terms of the current view on systemic JIA, I think you testified that it is autoinflammatory, correct?

A Correct.

Q In your second report, which is Exhibit 27, and you testified to several of these articles, you seem to discuss Exhibits 12, 13 and 15 in your discussions to support implication of infection and/or vaccine as triggers for JIA. Is that correct?

A That's my recollection, yes.

Q Okay. The first one was the Prakken article, which is Exhibit 12. Now, you would agree with me that Prakken in the context of this article indicated, and I'm reading here:

"Infections and vaccinations have been suggested as two candidate triggers, but neither has been confirmed because of the scarcity of proper control perspective studies."

A That's from the Prakken article, correct. Exhibit 12. And I think it was one of my slides that I had in my direct.

Q Right. And it goes on to talk about the negative studies found with the meningococcal vaccine and the MMR vaccine in JIA.

A Negative, inconclusive, but sure.

Q Right. And those are also part of the record as well, correct?
A Correct.
Q And would you agree that such proper control perspective studies are usually done when there's enough case reports reporting a connection between a certain disease process and a certain element such as a vaccination occur?
A That's one avenue to drive doing those types of studies. That would be the avenue that is driven by clinical science, but not necessarily the avenue that would be driven by basic research. That's not to say that there's -- again, there's categorization there, but that's not to say that there's a void and there's a lack of communication between the two. But certainly I would agree with you that case reports would be one way or one factor that would trigger an additional study to be done.
Q And there are no case reports filed in this case indicating a practitioner reporting a connection observed between the HPV vaccination and systemic JIA, correct?
A Nothing filed here. Nothing that I recall seeing. I don't recall. I'm sure -- I should say reasonably sure -- that I would have found a case

report in my methodology and my background looking for this information, and I don't recall finding anything.
Q Did you say that you don't think you would have found it based on --
A No. I said I think I would have.
Q Okay.
A And I just don't recall that I did. Sorry.
Q That's all right. That's fine. And then another piece, and I think you alluded to this during your direct examination, would be looking for epidemiology to support a connection, correct?
A Yes.
Q And there's no epidemiology here?
A There's no epidemiology that's meaningful enough to inform us on the information.
Q Switching to the Mellins article, which was also cited by Dr. Rose in his report, quoting from Mellins it states, "Consistent with the possibility of infections and infectious triggers, onset of SJIA seems to be seasonal in some studies."
And I think you pulled that quote out as part of your supplemental report and put it in your supplemental report. Is that correct?
A Let me check.
(Pause.)

Q Looking at page 6 --
A Yes.
Q -- of Exhibit 27.
A I did, yes.
Q The term "possibility of infectious triggers." Certainly the term "possibility" is a less than definitive term, is it not?
A Agreed. And the context there goes to specificity and the search for single infections or in this case single vaccines. And part of my opinion here is that that's not the issue.
People have been working on -- clinicians and basic research scientists have been working on -- this problem for a long time, and the level of consideration of association of mechanism to disease outcome is at the level of the immune response and in this case proinflammatory cytokines. So what I'm saying is that the element of the disease that in my mind should be being tracked in epidemiological studies in this issue would be elements of the immune response, including proinflammatory cytokines.
So I doubt, and to date we haven't. I doubt that we'll find that there's particular infections that drive the disease, that there's particular vaccines. It's complex. It's a multifactorial

disease that has many genetic factors, as well as environmental triggers, and those triggers are general. They're not specific, and they're working at the level of the immune response.
THE COURT: Dr. McCabe, in the first sentence of that answer you said clinicians and basic researchers have been working on this problem for several years. When you say "this problem," what's the "this problem"?
THE WITNESS: The problem, this problem being causes of systemic juvenile idiopathic arthritis.
BY MR. WISHARD:
Q And in the abstract -- I'm just quoting from the abstract -- it says, "The triggers of disease are unknown, although infections are suspect," agreed?
A Agreed.
Q And then at the end of the article -- we're at Exhibit 13, page 8 -- the beginning of the last paragraph of Conclusions, it says, "A number of additional questions are raised by the available data." The first one is, "What are the initial triggers of SJIA," correct?
A Correct.
Q So I guess as the title of this article

illustrates, it answers some questions or provides some answers, but there are a lot more questions than there are answers?

A It does. That's one place in that article that you've cited, but on page 1 right in the abstract -- one, two, three, four -- four lines down if you pick up where it says, "Once initiated..." --

Q Yes.

A "Once initiated, systemic JIA seems to be driven by innate proinflammatory cytokines."

Q Seems to be.

A Seems to be, but sure. Seems to be. I think that the weight of the evidence is that they play a prominent role in the disease.

Q And then if you could switch to Exhibit 15, which I don't think you talked about during your direct examination, but you did talk a little bit about in your supplemental report. This is I think it's Ronaghy, R-O-N-A-G-H-Y, article.

A Sure.

Q I'm looking at page 1 of that almost to the bottom. It says, "For example, in juvenile idiopathic arthritis a temporal relationship between disease onset, childhood vaccination, remissions in flares hint at a possible relation of JIA disease activity

and vaccinations or infections."

A Yeah. Agreed. And that's what it says. So the operative word there is hint. Again, it goes back to what I said earlier is the hint is coming from that these -- what's the commonality is that many of these provoke the immunological events that are ascribed to the disease, systemic juvenile idiopathic arthritis.

That's what the hint is, and the specificity isn't at the level of individual vaccines or individual infections because of the trigger or at least the environmental trigger. No debate, no argument from me, that there also are genetic predispositions and genetic factors underlying the disease, but those are multigenic and diverse.

You know, so I'm not saying -- part of my opinion is not saying that everyone who gets Gardasil or everyone who gets a mycoplasma infection or everyone who gets a trigger of these events is going to develop the disease. It would be difficult, given the multigenic, multifactorial nature of the disease to determine that.

Q And the Ronaghy article, Exhibit 15, really dealt with polyarticular and oligoarticular JIA, correct? It didn't deal with systemic JIA.

A That's my understanding. Correct.

Q Are you aware of whether anyone is looking at some type of case control study whether the HPV vaccine plays any role in systemic onset JIA?

A I am not.

Q Now, my understanding is that your medical theory of causation -- I'm done with that article. Thanks. Your medical theory of causation in this case is a proinflammatory cytokine milieu stemming from the HPV vaccine leading to systemic JIA. I think that's in your reports, correct?

A That's fair, yes.

Q And to support that I think in your reports, as well as your testimony today, you cite Exhibits 26, 28, 30, 32 and 34 as the main articles that you're relying on to support your opinion. Is that correct? I know you've cited to others, but those are the ones you talk about.

A Well, I have references. You have exhibits. I just needs to catch up to your --

Q Sure.

A Ask me the exhibit numbers again, please.

Q Sure. Let's start with Exhibit 26, which is the first Pinto article.

A Sure.

Q The one from 2005. You would agree with me

that this Pinto article does not mention arthritis in general and does not mention SJIA specifically, correct?

A As far as I recall. Correct.

Q And it doesn't mention anything about the theory proposed here of a cytokine reaction from HPV vaccine leading to systemic JIA?

A It does not.

Q And I think you testified on direct examination about this study measured multiple cytokines, correct?

A Yes.

Q And the samples were treated differently. Some were whole blood versus I believe peripheral blood, mononuclear cells, correct?

A Yes.

Q And would you agree with me that the participants in this study did not experience any symptoms?

A I can't agree with you on that because the design of the study didn't capture that information. To be fair, to put your question in context I don't think that the investigators and the authors of this study had that in mind, that that was an outcome that they were studying, but since the article doesn't

speak to that and doesn't address that I can't answer your question affirmatively.

Q And this didn't actually study the HPV vaccine Gardasil that we're talking about here, did it not?

A It did not. It studied it was a related vaccine in that it was an HPV-16 L-1. It was expressed in a baculovirus and not as part of similar to the recombinant Gardasil vaccine that's produced in yeast cells, but nevertheless it was using one of the four components of the Gardasil vaccine to drive these responses, so it has some commonality.

Q And next if you could look at I think your Reference 17, Exhibit 28 in the case, which is the second Pinto/Garcia-Pineres article?

A And I seem to have put it out of order, so hold on.

Q Sure.

A I'm ready.

Q Okay. Again, this article, Exhibit 28, does not mention arthritis in general or SJIA specifically, correct?

A Correct.

Q And this study was looking at the cytokine patterns produced by vaccination to identify

biomarkers of vaccine response, correct?

A Yes, and one of those biomarkers, generally speaking, would be the cytokines and the proinflammatory cytokines.

Q Right. And multiple cytokines were measured similar to Exhibit 26?

A Correct.

Q Not the same ones, but --

A Some overlap. Some overlap. Some consistency in experimental design.

Q Right. And I think the authors of this study specifically noted that the results may not directly be extrapolated to cytokine patterns that will show up in the commercial vaccine, Gardasil, because it wasn't used in this study.

A I don't remember that specifically about the article. It wouldn't surprise me. It's not an unreasonable thing for them to have concluded. You know, science is about precision, and this is a different vaccine or immunogen than Gardasil so that's a variable.

Q Just looking at Exhibit 28, page 5 at the bottom, the next to the last paragraph, it talks about, "Results obtained in this study may not be directly extrapolated to the cytokine patterns that

will be obtained after vaccination with the commercially available L-1 VLP vaccination because participants in our study were immunized with VLP without an adjuvant."

A I'm sorry. I didn't track where you were quoting at.

Q Sure.

A Is it in the Discussion?

Q It's at the very end before the Acknowledgements and References, two paragraphs up, Exhibit 28, page 5, where it says, "Results obtained in this study..."

A Correct. May not be directly extrapolated is correct.

Q Okay. And I think the next study you talked about was Exhibit 30, which was the Evans article, correct?

A I believe so.

Q Okay. Which is your Reference 19.

A Okay.

Q Now again, this article does not mention arthritis in general or SJIA specifically, correct?

A Correct.

Q This study involves several faculty members from the University of Rochester School of Medicine

and Dentistry, correct?

A Certainly I know Robert Rose, so the answer to that is yes. Some of these individuals I know, some of them I don't, so the answer is yes.

Q And you weren't involved in this study at all in your capacity when you worked at Rochester as a full-time professor or as an adjunct professor? Let me see when this was. This is 2001.

A 2001. So this work was likely done before I arrived at U of R and published in 2001 so, no, I wasn't. I wasn't involved.

Q At the bottom of the first page it talks about the University of Rochester Vaccine Center. When you arrived at U of R until really today as an adjunct professor, are you involved at all in the Vaccine Center?

A Peripherally. I was not -- and so it's a center. It's not a department. I didn't have an adjunct appointment in the Immunology or Vaccine Center involved in that. I was working at the University of Rochester Environmental Medicine in conducting research and immunology, immunotoxicology, certainly having a strong academic environment and colleagues in the Vaccine Department, Center for Vaccine, served on student committees from students in

that department, served on committees and academic committees with members of the Center for Vaccine.

Members of the Center for Vaccine were part of the Immunopathogenesis and Immunomodulators Core that I talked about that were part of the environmental health sciences center. I collaborated with Bob Rose on the HPV lead study that I talked about earlier. His laboratory was active in doing the antibody titer work that was part of that study.

And so not in a way, not in a direct way where I had a faculty appointment there, but certainly in a way that was appropriate for an academic institution like the University of Rochester.

Q You didn't mention any of that in your CVs that were filed in this case, though, did you?

A I don't know how I would put that into my CV. I mean, that's one of those things. I mean, I'm sorry. Maybe I didn't understand your question. What are you asking me that I didn't put in my CV?

Q The information regarding your activities regarding the University of Rochester Vaccine Center.

A No, I didn't, and I'm not sure what the relevant portion of an academic even in the capacity that I'm serving now that would capture all of those additional things that one does in their professional

career that doesn't document publications, grant activities, teaching and things like that.

Q Now, this study, the Evans study, Exhibit 30, involved the Gardasil vaccine, correct?

A I believe it did.

Q It's specific for HPV-11 virus, which was one of the viruses covered by Gardasil.

A Correct.

Q And this study, Exhibit 30, also had the adjuvant as part of it as well, correct, the vaccine?

A I don't remember that detail, and if you can direct me to the paper.

Q Sure.

A The part in the paper that -- it does. I have it. Under Study Design. So, yes. It contained an aluminum, a metal adjuvant as part of the vaccine.

Q Which is the adjuvant --

DR. ROSE: Adjuvant.

MR. WISHARD: Adjuvant. Thank you.

BY MR. WISHARD:

Q -- contained in the Gardasil vaccine?

A The adjuvant contained in Gardasil vaccine is amorphous aluminum hydroxyphosphate sulfate. The adjuvant that's used here is aluminum hydroxide or alum. So there's a commonality in that it's an

aluminum or alum-based adjuvant, but it's not identical.

Q Okay. And on page 5 of Exhibit 30 at the top right-hand column it says, "The results clearly demonstrate that this HPV vaccine preparation formulated in an aluminum hydroxide adjuvant is safe, well tolerated and highly immunogenic in healthy seronegative volunteers," correct?

A Correct and agreed.

Q If you could flip now to 34, which is the Chao article. Okay. In this study they didn't look at necessarily JIA, but they were looking at JRA, correct? I'm looking at Exhibit 34, page 5, on the table. They were looking at juvenile rheumatoid arthritis.

A Correct.

Q And you cited this article to support your opinions regarding the appropriate timing of vaccine causation here, correct?

A I cited this article for two reasons. That's one of them.

Q Okay. And the other reason being what?

A That part of the methodology that I followed was to address that aspect of the Hill criteria, which is strength of association as revealed by epidemiology

studies.

Q And then the conclusions, which are part of the abstract. It says, "No autoimmune safety signal was found in women vaccinated with HPV-4," correct?

A That's correct.

Q Would you agree with me that -- I'm done with that. Thank you. Would you agree with me that none of Vanessia's treating physicians, either Dr. Ragala or Dr. McCurdy, stated a belief in their records that her systemic JIA stemmed from her receipt of the HPV vaccine?

A My recollection of the records, medical records, is they didn't state an opinion one way or another.

Q And after Vanessia had her onset of symptoms post the second HPV vaccine, you would agree with both Dr. Ragala and Dr. McCurdy allowed her to get the third HPV vaccine, correct?

A You're asking me to -- I think you're asking me a question there that I'll tell you I think goes outside my expertise because I'm not -- it depends on how you're asking me that question. So what I'm being careful about here is I'm not a physician so, I mean, I'm not making a clinical determination there whether they did the right thing or the wrong thing by giving

her that vaccine. I just want to make sure that that's not where we're going there.

Q Just let me ask you just a general question. Did you see anything in the records that indicated that either Dr. Ragala or Dr. McCurdy had any concern about giving --

A As I said, I didn't see one way or another. Correct.

Q Any concern about going forward and giving her the third vaccine?

A Didn't see anything that addressed that.

Q Now, you talked about Vanessia's condition post the third HPV vaccine. You would agree that she saw Dr. McCurdy on September 3, 2008? I'm referring to Exhibit 5, page 45.

A I have notes about that. If there's something about the actual exhibit, I don't have that here.

MR. WISHARD: Okay. Do you have that to give to him?

MS. O'DELL: I do. What page did you refer to?

MR. WISHARD: Exhibit 5, page 45 to 46. Thank you.

//

BY MR. WISHARD:

Q I'm looking particularly at Exhibit (sic) 45 at the top under where it says History, History of Present Illness. I'm just going to read here a quote and see if you agree with my interpretation or reading of this I should say. It says, "Some improvement on Enbrel, but patient stopping Prednisone rash returned." I think I read that correctly.

A I agree.

Q So is it your understanding that in the interval at least from the last time Dr. McCurdy saw Vanessia before September 3, 2008, she had stopped Prednisone for a period of time?

A Yes. So just to be clear on my opinion here, and I think I stated this earlier, is that there's multiple variables here. We have Enbrel coming in. We have Prednisone coming out. We have her receiving a Gardasil vaccine. And so it's difficult, having at least three variables there, to ascribe any of the clinical presentation or changes that she had, or if you phrase it as exacerbation of disease or a flare, to one, two, any combination of the above.

Q I'm done with that. Thank you, sir. Assuming that we can agree hypothetically that the HPV

vaccine does elicit some type of proinflammatory cytokine response and it did so in Vanessia here, what evidence do you have presented today either in the exhibits that have been filed or your testimony that would take the next step to show that that inflammation or that response, elicited response, caused Vanessia to suffer from SJIA as opposed to just obtaining it because she was a teenage girl and happens to be right in the appropriate time period for the onset of systemic JIA?

A So you're asking me to make an assessment between anything can happen versus this is an individual who received a potent immunogen that drives these cytokines, these innate responses and these inflammatory processes.

In the timeframe that she was receiving these vaccinations, although the cytokines themselves are not being measured, the clinical indicators of what I'd expect to be driven by the cytokines were being found, and I've talked about those in terms of her presentation with fever, with rash, her joint pain, her elevated acute phase proteins. All of these are attributed to the cytokines, the proinflammatory cytokines that I've been discussing.

Q But that would occur if she hadn't got the

vaccine, but she got SJIA.

A Well, we don't know that. We don't know that. What we know is that she had gotten the vaccine during that time period.

Q Well, we know she got SJIA and we know that SJIA shows a tendency that certain cytokines are activated, correct?

A Correct.

Q And we know that the vaccine has certain cytokines that are activated, according to your testimony, correct?

A Correct.

Q If Vanessia had not received the vaccine in this case, taking that out of the equation, would you be able to identify a cause for her SJIA based upon everything in the record but for the information that she got vaccinated?

A The answer is I don't know. We can't answer that.

Q But certainly the timing is important to you.

A Well, the timing is important and the timing that she got that vaccine. In my opinion, my opinion is the vaccine caused her to develop the disease at that time.

I'm not arguing that or I'm not proposing that Vanessia Koehn wasn't somehow predisposed to the disease or had what we would perhaps agree would be a genetic predisposition to developing the disease, but her development of the disease, manifestation of the disease, required a trigger, and the most obvious trigger not just based on a temporal association, but based on the biology and the immunobiology of that trigger in the context of everything else we know, and we don't know everything, but in the context of everything we know about systemic juvenile rheumatoid arthritis, was Gardasil.

Q And you provide that opinion today without any case reports that are supportive, without any epidemiology that is supportive and without any case control studies that are supportive of your theory of vaccine causation here that basically look at this issue either on a case level, in a case report, on an epidemiological level or in a large study?

A And my answer is yes, I do, because it's the only way of getting at that problem of how -- the problem again being how this disease is triggered, this disease being systemic JIA, in this context. It's not surprising to me, given the rarity of this disease, that there are not appropriate

epidemiological studies that would be able to make that determination, so there's an absence of epidemiological studies.

It means that one criterion of the Hill criteria is missing, and admittedly from the perspective of a scientist that would be something nice to have, but then you have to step back and have to understand how difficult it would be to obtain that information. So what I'm saying is the absence of information doesn't inform us here in any way.

Q Are you saying that no one is looking at this question right now, to your knowledge?

A What I'm saying is the information is not available to me to be able to use it in my analysis.

Q Is your theory something that you have observed being discussed generally in the immunology community, that the HPV vaccine can cause SJIA?

A No. I mean, what I've been involved in in the general immunology, toxicology, immunotoxicology community, the community of scientists interested in disease causation, is what I spoke about earlier today, is environmental factors in the context of autoimmune diseases in general.

MR. WISHARD: Sir, that's all the questions I have. Thank you.

THE COURT: Dr. McCabe, let me begin by again thanking you for participating today and --

THE WITNESS: Thank you.

THE COURT: -- coming down to Washington and testifying here. Can you explain the process that led to you preparing your initial report? How did you go through that? I imagine that it starts with a phone call from Ms. O'Dell --

THE WITNESS: Oh, sure.

THE COURT: -- or someone from Ms. O'Dell's office. I kind of assume that because you're here with Ms. O'Dell so --

THE WITNESS: Okay.

THE COURT: -- I figure that there has to be a phone call or an email like that. And from that how did you first hear about the case to when you wrote your first report? Can you explain to me what you did in that process?

THE WITNESS: Sure. So Ms. O'Dell's office sent me some materials, medical records. I think that's really all that was sent to me was the medical records, and we had some conversations about much in line with what we talked about here today in terms of my background and some of the big issues in the case.

She asked me to look at those materials and

to investigate whether there was a tenable scientific argument that could be made to support that Gardasil caused or was a substantial contributing factor in Vanessia Koehn's disease. My approach there is I approached it as a scientific undertaking. That's a hypothesis. Gardasil causes Vanessia Koehn's disease. What's the disease and what do we know about the disease? I had some understanding of the disease but did some additional research to understand some of the details that I think are important.

So a hypothesis is offered and then test the hypothesis. So the first hypothesis is Gardasil causes disease. Well, what information exists in the scientific literature? And that's really the testing that's being done. It's an analysis and it's a process. It's a scientific process during this time period where I didn't feel it required me to go back to my own laboratory or get with my colleagues and design experiments to test that.

It was an endeavor to what's the information that would weigh in at that level. And as we've discussed here, there's not very much that would weigh in on that level. So I drew on my background and some of the other activities that I've been involved in, some of the things that I've talked to you about

today, earlier today on advisory boards that I've served on where these same types of general issues are discussed and how to take epidemiology, for example, to the next step to molecular epidemiology, to marry basic science with immunology.

And the rubric there is rather than focusing on diseases as the end point focus on elements of disease or biomarkers of disease as has been discussed here. So really the marrying here is the marrying of basic mechanistic science with epidemiology and human population studies.

These are things that I was doing while I was at Wayne State, for example, and working with certain epidemiologists there, and some of that's on my CV, but really it was to build on my background and say what are the elements of the disease process and considering that one of the chief elements of the disease process is the elicitation of proinflammatory cytokines and to really focus this analysis then on well, what's the evidence? What's the data that supports that Gardasil vaccine causes an increase in those proinflammatory cytokines?

And again, that involved a hypothesis and testing of that hypothesis through publications that are in the scientific literature, much of which, if

not all of which at this point, are in my reports and in my testimony.

THE COURT: And about how much time did you spend reviewing scientific literature? I understand you don't know exactly, but can you give me like an order of magnitude?

THE WITNESS: Sure. So as of this week, so before -- there's been a lot of time spent this week. So you appreciate that. Before this week, Ms. O'Dell contacted me I believe in April of 2011, and the total hours that I've put into this case up until this week in researching articles, writing a report, writing a supplement report, reviewing any of the materials, the medical records, was about 40 hours. So about a week's time, a week's professional time.

THE COURT: And we talked about your background. Do you have any specific training in epidemiology?

THE WITNESS: Just what I pick up by myself. I mean, I don't think I ever took a course on epidemiology. I certainly took statistics courses so that's important, an important component of epidemiology. Some of my coursework either in infectious disease, in microbiology and immunology in graduate school, toxicology, involves a fair amount of

epidemiology, some of which would have been in didactic coursework, but really also informally through associations with other epidemiologists.

So I don't hold myself out. I think the direct answer to your question is I don't hold myself out. I mean, I've got enough hats I think as being a toxicologist and immunologist. I understand a fair amount of epidemiology, but I don't hold myself out to be an epidemiologist.

THE COURT: Before you started work on this case had you done work on the HPV vaccine? Were you familiar with that at all before you worked on this case?

THE WITNESS: Yes, I was familiar with it, as I talked about earlier today, in the pilot project in the environmental health science center, that we had a project ongoing. So I had an understanding of what Gardasil was.

And also, and I think I said this earlier today, is that this is a DNA virus, papillomaviruses. In fact, when I was at Albany Medical College papillomaviruses and polioviruses were a big focus of that research program, as was discussed here in the Evans article with some investigators at U of R.

Those investigators, many of those

investigators have worked on HPV vaccines and so within those academic environments I knew much about the virus itself, the virus as well as the vaccine.

THE COURT: Do you have any other background with other vaccines like MMR or --

THE WITNESS: Sure. I mean, as you know, and really just in a testifying sense there is that I participated in the omnibus proceedings for autism, which involved the MMR vaccine, and as other vaccines and experimental models that I've been peripherally involved in, but again I wouldn't hold myself out to be a vaccinologist.

THE COURT: I think you might have covered some of this, more of this in your background with Ms. O'Dell, but have you functioned in a process of like reviewing grant applications that NIH or some other institution has a source of funding and there's five proposals and someone has to decide we have enough money to do two, so someone is going to pick two of the five? Have you worked in that --

THE WITNESS: Sure.

THE COURT: -- capacity as someone who like selects proposals for funding?

THE WITNESS: Yes. Something for you to understand is the process of peer review. And anyone

who's ever served on an NIH peer review panel or a DOD panel understands that we never use the F word. What the scientists are doing at that level of peer review is determining the scientific merit. Based on our work in determining the scientific merit, it's left to other people to decide what to fund.

And so obviously there's a correlation between those proposals that are judged to be more meritorious than other proposals, but the funding decision is made at a different level, not by the scientific peer reviewer, so not something I'm involved in, and appropriately so. And part of that is because they know what the dollars and cents are for funding levels. They know what the priorities are for their particular funding agency for problems that they may be more interested in.

THE COURT: So in that capacity at DOD, how do you rank or evaluate competing proposals?

THE WITNESS: I'm sorry. Just to give you insight and improve your understanding, the other thing that we're cautioned to do, and I do a lot of this -- I do it very well and understand the process -- is the proposals are not actually at the level of scientific merit review competing against each other. The analysis is against and the analysis of merit is

against some imaginary gold standard.

So never during a proceeding like that we wouldn't be saying something like well, this is a better proposal than that proposal or something like that, but human beings being who they are, some of that's implicit in some of the reviews. And how does that work? It works by those proposals that -- I think really what you're asking me is how do you determine scientific merit.

How do I determine scientific merit? It's based on whether a cogent hypothesis has been stated, and really what I'm about to talk to you about is the analysis of scientific merit is an analysis of how well does this proposal follow the scientific method. Is there a cogent hypothesis that's proposed? Is that hypothesis well-grounded in the background information?

Is there an appropriate experimental design to test this hypothesis? Is there any preliminary data or preliminary information that would hint or provide some indication that this is a hypothesis that's worth pursuing and is going to be pursued correctly and the data are going to be analyzed appropriately?

And I guess the third or another aspect of

it is to consider the relevance of the proposal to society. So what? Who would care whether this type of research was going to be done and how much would it cost? That's one thing that is part of the scientific review process is to take a consideration of how much would a study like this cost to do and is it feasible based on the cost?

THE COURT: In terms of basic science and the immune system, we've talked about a few specific cytokines like TNF alpha and IL-1, IL-6, and I know that the Pinto article has columns of cytokines.

THE WITNESS: Sure.

THE COURT: But my understanding is that Dr. Rose has the opinion that there's only a limited number of cytokines, that there's only so many ways that the human body can respond to things by generating cytokines, so that the fact that Gardasil prompts IL-6 and IL-6 might be implicated in the pathogenesis of SJIA is kind of a coincidence just because we use IL-6. There's only so many.

I'm not sure how many medical cores (phonetic) I have going on here, but there's only so many tools in our toolbox, and IL-6 is one of them so it gets used for a lot of different things and it doesn't necessarily have a causal relationship. So

how would you address I guess the limited point like the number of cytokines, like the degree of variability and like how many different tools can we draw upon when we need to respond to an antigenic challenge?

THE WITNESS: Well, building on the way you asked me that question, just because there's a limited number of tools available to get the job done doesn't mean that that tool doesn't have a role in getting the job done. There's a limited number of ways to pound a nail, okay? You know, all things being equal, if there's a hammer on the table and I walk away and I come back and there's a nail pounded in, my best determination is going to be somebody used the hammer to pound that nail in.

So I understand and accept to a certain extent that there is commonality in the immune effector functions. I talked about those both from the adaptive immune system and in the innate system, that there are effector mechanisms. You know, they're pretty broad. I mean, we're not just talking about a few. We're actually talking about another order of complexity, which is not just any one of these individual cytokines, but their appearance in time and in multiple combinations.

You know, that's a level of complexity that we're not able to approach addressing in this case given that Vanessia Koehn wasn't a research subject, all right? But just back to emphasize my answer is that I wouldn't accept it just because there is a perhaps finite number of cytokines that they're not involved as a mechanism or a common element in Gardasil and what should be protective immunity and systemic JIA.

THE COURT: I think that SJIA must be caused by something other than or in addition to Gardasil --

THE WITNESS: Absolutely.

THE COURT: -- because SJIA existed 40 years ago, long before there was Gardasil.

THE WITNESS: Absolutely. Correct.

THE COURT: We don't know what that other thing is -- that's why it's idiopathic -- or if it's one thing or many things, but there's something besides Gardasil that causes --

THE WITNESS: Yes. And I think just in idiopathic, and I think I had alluded to that earlier is that it is many things. It is likely to be many things. I alluded to it earlier in my answers on cross and also I think in my direct.

And idiopathic in my mind also means that

that's that individual patient's presentation, and I think that's worthy of consideration here is that what we're really talking about -- worthy of consideration in the context of epidemiological studies and the difficulty in doing the studies and interpreting the studies is we'd have to be studying Vanessia Koehn disease, if you're understanding what I mean.

She likely has -- I mean, she does have -- a unique genetic background. There may be some overlap between her and others who have the disease in certain genes, but given the complexity and the multiple factors that are contributing, together with many environmental insults and not just Gardasil, that's a level of complexity in designing those types of epidemiological studies.

Generally as scientists and clinicians, are we moving towards and do we have the types of tools that will allow us to undertake those kinds of things? Well, sure we do. That's what the whole genome project and all of that weighs in on.

THE COURT: So if you were back at U of R and somebody came to you and they wanted to have a thesis and they wanted to say Gardasil causes systemic juvenile idiopathic arthritis, that's their hypothesis. How would you advise your graduate

student to test that hypothesis?

THE WITNESS: The sky's the limit in funding, right?

THE COURT: Sure.

THE WITNESS: Sure. Absolutely.

THE COURT: We'll start there. We'll work down. It's a thesis. We can dream big.

THE WITNESS: The sky's the limit in funding. So I would highly advise them to think back to Bradford Hill criteria from my slide. I would advise them -- essentially I would advise them -- to take the same steps that I did and let's make this better.

There's no argument there they could make this better and inform better, so I would say start there and let's design some epidemiology studies. Let's do a power calculation as to how many individuals would we need to have in that study to see a meaningful change in disease incidence. I would tell them in addition to doing that to look at the levels of the elements of the disease and use as sophisticated methods as possible to look at markers of disease, genetic markers of disease, cytokine markers of disease.

I would tell them that they're going to need

a lot of help in terms of collaborations because no one graduate student or one scientist as their mentor is going to be able to conduct an epidemiology study with hundreds of thousands of subjects to collect samples from them, to have those samples analyzed, to do molecular analyses as I alluded to to look at genes, to look at changes in cytokine levels, to get approval from IRB, internal review boards, to do that kind of human subject testing.

You know, if the sky is really the limit I would tell them to possibly look for some changes in animal models to integrate with the epidemiology human subject stand. So it would be a huge undertaking. There's no question about it.

THE COURT: Do you know if there are animal studies for SJIA?

THE WITNESS: To my knowledge, there are no animal models of SJIA. As I said, animal models. Something that may be in -- you know, I'm just kind of shooting from the hip here, but there may be animal models. There may be ways of integrating animal research to look at responsiveness to the vaccine and the production of cytokines, how those cytokines might be modulated by the vaccine under various conditions or something like that. And the reason for mentioning

animal studies in that context is that you can control the variables much more readily.

THE COURT: So you talked about when you were asked the question about your evaluating of the grant proposals, you talked about like you'd want to see like how reflective they were of the scientific method. And one thing I remember about the scientific method is that you propose a hypothesis and then you can try to falsify it and then prove the negative.

THE WITNESS: Sure.

THE COURT: So is the hypothesis that Gardasil causes SJIA, is that falsifiable?

THE WITNESS: Sure. Yes. I'm trying to think of a readily way to make it. For the first level, and I did this, you know. So the answer is yes. Did I as a scientist executing the scientific method and knowing that that's a key component of the scientific method did I do that? Yes, I did.

I did that, for example, by proposing or posing the hypothesis are there human population studies to support this association. So that goes towards addressing whether it's falsifiable. So it's inconclusive in that regard, but it would have been falsifiable if there, in my opinion, were adequately powered, appropriate epidemiological studies that

looked at that specific question.

THE COURT: But in some ways the qualification adequately powered, I'm not sure if that gets to the falsification aspect of it the way I'm thinking of it because from what I understand you can never disprove something with epidemiology because you could have an epidemiological study with 100,000 people, which would be 100,000 controls, which would be a huge cost.

THE WITNESS: It would be a huge cost, and as my understanding of the incidence of the disease you would expect to find one case.

THE COURT: Right. So then you would say like that's not adequately powered, so then it's like you need an epidemiological study with 10 million people and 10 million controls. That would give you one result, and you would say well, that's not adequately powered because then you would need to do 100 million with 100 million controls.

THE WITNESS: Sure. Right. So again thinking back to the Hill criteria and cohesiveness and consistency between studies, yeah. Just having one epidemiology study wouldn't necessarily be informative, but geez, I think it would be a huge step in the right direction. Are there other ways of

falsifying? Are there other ways of falsifying the findings here, the opinion, or generally to falsify a hypothesis? Sure.

If in the timeframe that Vanessia was being vaccinated whether any of these immunological markers were being tracked in time in the context of the illustration of her disease. And here we don't know. We don't have that data, so we make use, in my opinion and in testing my hypothesis and testing it with in my mind the best data that are available to test it.

THE COURT: With reference to the Bradford Hill criteria, and we can go through them. One of them is strength. How strong is the connection between Gardasil causing the SJIA?

THE WITNESS: I mean, you can't address it because there's no -- so strength of association means in an epidemiological study, for example, was there a twofold increase? Was there an odds ratio of two? Was there a twofold increase? Or even in my opinion in cases anything above one, but there's a tight confidence interval, that would go to strength of association.

But in the studies that have been conducted to date there's no epidemiology studies focused specifically on SJIA, and in the studies that have

looked at autoimmune diseases in general the strength of association is present and is not indicative of Gardasil causing autoimmune diseases in general.

THE COURT: So it would seem like taking just one of the Bradford Hill criteria, and I've read the articles. I know that one of them is not dispositive, but it seems like the strength criteria, that would be on the minus side.

THE WITNESS: In support of his hypothesis. Absolutely.

THE COURT: And then how about on consistency?

THE WITNESS: So there's a number of -- so again, as long as you understand that you're asking about autoimmune disease in general and Gardasil and autoimmune disease in general. And there's a reason for doing that, right, because when you talk about autoimmune diseases in general and you link all these autoimmune diseases together your incident rate increases, so therefore your sample size can decrease. Hopefully that's clear that there is consistency amongst the studies that have been done.

And this has been done both postmarket from studies that have been done and been published, some of which have been cited either by me or by Dr. Rose.

It was done in the premarket by the manufacturer. Dr. Rose, for example, has a table from that, as I understand it, in his report.

But there you're only looking in that particular table only looking at 20,000 individuals split in half between immunized and placebo and looking at general -- multiple autoimmune diseases, and the data and interpretation of the data goes to the general interpretation about autoimmune diseases in general as something to be concerned about with Gardasil vaccines. But given that it's only 10,000 or 20,000 individuals, you wouldn't expect to find SJIA jumping out in those data.

THE COURT: On the analogy part of the Bradford Hill criteria I was wondering if you could use the studies involving the MMR vaccine in JIA and the studies with the meningococcal vaccine in JIA, if they both serve as --

THE WITNESS: Yeah, you could. Sure. And that's how I applied analogy in my analysis. You know, that's a reasonable hypothesis or related hypothesis, an analogous hypothesis to consider with a few caveats.

You know, we've just changed a variable so now we're talking about a different vaccine and not

Gardasil. We're talking about vaccines that are not inducing an immune response that has the potency over and above the natural infection that HPV vaccine versus HPV infection has. The studies are done in individuals who already had the disease and may be having treatments, and really what you're looking for there is flares.

So, sure. At one level is this a way of disproving the hypothesis? And given that whether the data were in favor or not in favor of the hypothesis you still have the same caveats, that there's changes in variables, there's changes in the target population and the attributes of the target population in that you're talking about now a different vaccine that's eliciting an exacerbation of the disease for somebody who already has existing disease versus someone who at the time that Vanessia was first vaccinated didn't have or wasn't manifesting disease as best we can tell by the record.

So the other way I considered those issues was to consider at the level of the cytokine production. So the MenC vaccine is a vaccine against a neisseria meningitidis, so it's a bacterial infection, not a viral infection. The vaccine doesn't elicit the same type of proinflammatory cytokine, as

far as I can tell, as Gardasil does and so maybe at the level of -- not maybe, but my conclusion in not allowing the MenC vaccine studies to inform my opinion in this or change my opinion in the connection of Gardasil to SJIA was it doesn't appear to act through the same mechanisms of disease or elements of the disease as I've been describing it.

I mean, the other thing is the MenC vaccine is to a polysaccharide antigen, so it's expected to interact and drive B cell antibody production through that, through those types of mechanisms.

THE COURT: Do you know what cytokines the Menococcal C vaccine elicits?

THE WITNESS: As I sit here right now I don't. I don't. I don't have that information.

THE COURT: Do you know what type of cytokines the MMR vaccine elicits?

THE WITNESS: No, I do not. I think, if I could, I mean, this is related to -- what I'm discussing here is also related to the mycoplasma, pneumonia. At least there's an abstract here and maybe some other information that mycoplasma infection -- infection now, not vaccination -- has been implicated in SJIA. Mycoplasma elicits many of the same proinflammatory cytokines that we've been talking

about in the context of the disease, SJIA, as well as elicited by Gardasil.

THE COURT: In the Verstraeten article, which is I think Exhibit B --

THE WITNESS: Uh-huh.

THE COURT: So I have a note here on page 6633, which is the fourth page of the document. Okay. The discussion begins:

"Bearing in mind the background incidence of autoimmune diseases in adolescents and young adult population, it seems likely that with broader use of HPV vaccines or other vaccines targeting this age group autoimmune disorders will be reported in temporal association with vaccine administration even in the absence of a causal relationship."

So how do you respond to that statement, which seems to suggest it's more a coincidence of timing than an actual causation?

THE WITNESS: My response to that is that as a scientist that's not the appropriate way to vet that issue. There's an inherent bias in performing a epidemiological study that would be based on that type of a -- you know, essentially a way in to determining that should be done.

THE COURT: What's wrong with the statement?

THE WITNESS: Well, there's not necessarily anything -- well, let me see here.

THE COURT: So why is that showing a bias?

THE WITNESS: The statement doesn't show bias. The solution to the statement, which is -- so the statement is, "Autoimmune disorders will be reported in temporal association with vaccine administration even in the absence of a causal relationship." In order to understand that there's an absence of a causal relationship one would have to do an appropriate epidemiological study, and my opinion is that that would not be the appropriate study group to conduct that study in because of the bias inherent in those who are reporting a disease coming into an epidemiological study.

So there's no randomization. There's no case control structure to that type of a study. So I guess what I'm saying what's wrong with the statement is the part about even in the absence of a causal relationship. In my mind it's an assumption that there's no causal relationship, and what it's saying is that no causal relationship established based on the available science.

THE COURT: If you'd turn to page 6637? Can you explain to me what Figure 1 is showing?

THE WITNESS: Yes, I can. It's a figure that's addressing the relative risk of developing autoimmune diseases that have been grouped into target organs, so these are organ specific autoimmune diseases, not for the most part systemic autoimmune diseases.

So these are organ specific autoimmune diseases, including thyroid diseases, which would include Hashimoto's thyroiditis, Graves disease, skin disorders -- that would include diseases like scleroderma, psoriasis -- musculoskeletal diseases -- that would include diseases like rheumatoid arthritis, myasthenia gravis -- gastrointestinal autoimmune diseases -- that would include things like inflammatory bowel disease, Crohn's disease -- and neuroinflammatory diseases -- that would include things like multiple sclerosis and other neuroinflammatory diseases.

And at least one AE is -- I don't know what that one is. I don't know what the AE is standing for.

DR. ROSE: Adverse event.

THE WITNESS: Sorry?

DR. ROSE: Adverse event.

THE WITNESS: Adverse event. And that could

mean lots of things without me going more into detail. But I'm not sure if that's any adverse event or an adverse event attributable to an autoimmune disease. But anyway, this is a relative risk meaning that there is a comparison between those receiving vaccines that include the adjuvant present in Gardasil -- that's what the AS-04 is, the aluminum hydroxyphosphate sulfate. 04 is an abbreviation for that particular adjuvant.

So a comparison between individuals who got vaccines containing the adjuvant or got the adjuvant compared to control, naive individuals, and then determining the relative risk of any of these diseases. If there is no risk then the -- if there is no effect of the adjuvant then the relative risk is one. And that's why you have a vertical line going through one up through all of these diseases.

And now with each one of these individual diseases, including the category of Other, by the way, there's a relative risk calculated based on the comparison between the adjuvant receiving group and the control group. How do you get the relative risk? Relative risk is a mathematical expression of the incidence of disease expected divided by the incidence of disease observed, all right, between the treatment

groups.

So there's an expected rate within the population that each one of these groups of diseases should be observed, and now if you stratify that group somehow -- in this case between those that receive adjuvant and those who don't -- how do things change? Anything above one is an indication that there's an increased risk. Anything below one is an indication that there's some protective role, which sometimes can happen.

In these analyses one doesn't just take the mean, which is what the points are in each one of these graphs, so you see that, for example, in Other just to the left of the vertical bar there's a dot, so less than one in Thyroid Disease below, Musculoskeletal a little bit to the right, and then what you're also seeing here is the confidence intervals, the 95 percent confidence interval, 95 being that it's a statistical determination of what's the degree of error or what's the chances of being wrong in this analysis.

And you can see that for certain of these diseases there's very tight bars, bars being these lines that are going to the left and right with the hashmarks, and in something like the neuroinflammatory

disease there's a very broad bar, meaning that -- so here's what that means. For example, in the -- what's a good one to pick out here?

In the Musculoskeletal Disease the risk of -- and for each of these there's two bars for each of these groups, and that's because there's different vaccines that are being evaluated. But if you just take, for example, the top bar in the musculoskeletal group you can see that there's a mean relative risk calculated for this group somewhere between one and two.

It looks like it's around 1.1, 1.2, something like that, and there's a 95 percent confidence interval that stretches from about a point to the left less than one, somewhere around .6, .7 perhaps, all the way up to a little bit more than two. What does that mean? It means that there's an equal chance that the relative risk of developing a musculoskeletal disease in response to that particular vaccine that contained adjuvant is just as likely to be 2.2 as it is .7. So since that relative risk goes through one, it informs us that there's no risk.

And the description that I just gave, if you track me, accounts for each one of these things. For example, in the neuroinflammatory, the

neuroinflammatory diseases, you can see that it's even that much more broad. It extends all the way up to six, so it's just as likely that it could be six as that it could be almost zero. So again, what that tells you is that there's a lot of variability in the outcome measure.

(Pause.)

THE WITNESS: And I should add given that variability one would seek to design an epidemiology study that would tighten that.

THE COURT: So I want to ask you about Vanessia Koehn's case specifically.

THE WITNESS: Uh-huh.

THE COURT: So the way I think about it we have like whether Gardasil can cause systemic JIA. Sometimes we refer to that as general causation. And I understand your theory has two parts to it, the first being that Gardasil elicits proinflammatory cytokines. The second part being that proinflammatory cytokines cause systemic juvenile idiopathic arthritis. So that's how Gardasil can do that, and then we have to look at what happens in Ms. Koehn's case specifically. So we know that something other than Gardasil causes SJIA because --

THE WITNESS: Correct.

THE COURT: -- it preexisted Gardasil.

THE WITNESS: Agreed.

THE COURT: And we don't know what that is. We don't really know if Ms. Koehn was exposed to that other thing or not. Since we don't know what it is, we don't know what to look for.

THE WITNESS: No, but we have reasonable insight into the elements of the disease and the mechanisms of the disease.

THE COURT: Okay. So that other thing, and we'll use maybe a silly example, is maybe drinking iced tea with lemonade -- it's a silly example, but we'll use that -- causes proinflammatory cytokines also, and those proinflammatory cytokines lead to SJIA.

So what I see is your reasoning focusing on the fact that she had the fever and stuff like that, the evidence of the proinflammatory cytokines. Then it seems like the situation is if you're in your bedroom at night and you flip the light and the light goes on, the light going on is going to be the equivalent of developing SJIA. Now, when we see the light going on we know that there is electricity in the wall, so light going on tells us that there's electricity, just like with SJIA we know the person

has proinflammatory cytokines.

THE WITNESS: Okay.

THE COURT: So if you trace that electricity path back, something stimulates or something generates that electricity, and it could be a windmill -- you know, the windmill spins -- or that same set of electrical wires lead ultimately to a coal-fired power plant. They're different. There's coal and there's wind, but they both generate electricity.

So why does the presence of the proinflammatory cytokines in Ms. Koehn's case, which we know she has because she develops the fever and the joint pain. We know she has those proinflammatory cytokines even though we didn't measure them. We know she has them. Why does that tell us that it leads back to the windmill and not to a coal-fired power plant?

THE WITNESS: The lights go on, and the lights going on is analogous to SJIA. There's electricity that goes through the wall. There's an electrical circuit that provides the power to make the lights go on. The analogy I think is improved if you allow me to that we don't really know how the lights go on. We think it has something to do with the electrical circuit that's present. And there's a

variety of sources of power to make that electrical circuit function, but more precisely to make the lights go on.

That there's some clue, whether it be the windmill, whether it be the coal-fired plant. There's some association between activities at those places and the lights going on, and I think the pathway is the proinflammatory cytokines or the wiring, the electricity. And all of that information informs us that there's some connection between the two, but now we're in a situation where we're not really appreciating what causes the electricity and for the power to go on because we don't know. Somehow we're blinded to it, and we don't know that there's a coal-fired plant. We don't know there's a windmill.

But somebody comes in and builds a nuclear power plant, a potent producer of electricity or source of electricity, and now the lights go on. And somehow, if you're tracking me there, that's me using your analogy to get at what I've been saying here as the cause/effect relationship.

THE COURT: But to say that the vaccine caused Ms. Koehn's SJIA, you're ruling out the existing, yet unknown, other cause.

THE WITNESS: I'm not. I'm not ruling it

out. What I'm saying is that it is a -- that she's somehow predisposed. She's initiated. That the vaccine alone doesn't cause the disease, that the vaccine elicited her disease to manifest at that time. That was the stimulus. That's what makes sense.

THE COURT: But people got SJIA without Gardasil.

THE WITNESS: Right.

THE COURT: So conceivably she could have gotten it without Gardasil, too.

THE WITNESS: Conceivably in the analogy we had the windmill could have provided the power.

THE COURT: So if we know that the windmill could have provided the power or the nuclear power plant provided the power, how are you able to rule out like the windmill? How are you able to rule out the idiopathic, yet -- I mean, idiopathic doesn't mean no cause. It just means unknown cause or multicause.

THE WITNESS: But at the same time it doesn't mean unknowable, and at the same time it doesn't mean that you can't make use of the available information to -- sorry -- shine a light on what's trying to be determined.

THE COURT: Right.

THE WITNESS: Right. And it's really at a

-- you know, what's the appropriate phrase? As a substantial contributing factor, whether it's more likely than not. You know, this isn't that Gardasil had to cause her disease, but in the context of what I understand this Court is supposed to be doing it's to consider whether there's a logical sequence of events that ties the vaccine to the injury.

THE COURT: I think those are all of my questions, but you're not quite out of the spotlight --

THE WITNESS: That's fine. Thank you.

THE COURT: -- to continue our metaphor. Ms. O'Dell, did you want to ask any followup questions from cross or from my questions?

MS. O'DELL: Just a couple of things, Your Honor. And do you mind if I just stand here?

THE COURT: That's fine, as long as the court reporter can hear you. It's probably easier if you sit.

MS. O'DELL: Oh, okay.

REDIRECT EXAMINATION

BY MS. O'DELL:

Q Dr. McCabe, just a few followup questions, and I want to go back to some questions Mr. Wishard asked you in particular in regard to one of the Pinto

articles, Exhibit 28. Mr. Wishard directed you to page 5 of that article, the last page, just before the Acknowledgement section.

A Results Obtained?

Q Yes.

A Thanks.

Q Mr. Wishard asked you about, "The results obtained in this study may not be directly extrapolated to cytokine patterns." Does that mean this study should not be considered in terms of the proinflammatory cytokine milieu caused by the HPV Type 16 vaccine?

A The Gardasil vaccine? No. In my opinion, no, it doesn't mean it should be discarded. It means what I said before, that there's a limitation given the variables on the study, but the data are valid and applicable to the argument that L-1 VLP vaccines induce the production of proinflammatory cytokines.

Q Then in regard to the Chao article, Exhibit No. 34, was SJIA considered as an end point in this particular publication?

A No, it wasn't.

Q And lastly, over the course of your testimony here today is it your opinion that Gardasil was the only cause of Vanessia developing SJIA?

A No.
Q And what is your opinion?
A My opinion is that Gardasil was a trigger, was an environmental trigger that worked in concert with other predisposing factors that make up Vanessia Koehn, and she was for all practical purposes a person who was prone, initiated to developing this disease, and receiving Gardasil at that time was the trigger that caused her disease to manifest at that time. And her disease may have manifested due to other exposures later or never, but we don't know. That's not knowable for a single individual.
Q In your opinion, was Gardasil as a trigger a substantial contributing factor?
A Yes, it was.
MS. O'DELL: Nothing further, Your Honor.
THE COURT: Mr. Wishard?
MR. WISHARD: Nothing, sir.
THE COURT: All right. I just had one question. In the Chao article, what diseases would be encompassed in the term juvenile rheumatoid arthritis?
THE WITNESS: I didn't hear you. I'm sorry.
THE COURT: In the Chao article, what diseases would be encompassed within the condition juvenile rheumatoid arthritis?

THE WITNESS: As I understand it, the diseases that are limited to immune inflammatory events that are localized to the joints.
THE COURT: Okay. All right.
(Witness excused.)
THE COURT: And with that why don't we take a short break. We can go off the record.
(Whereupon, a short recess was taken.)
THE COURT: Let's go back on the record. Mr. Wishard?
MR. WISHARD: Yes. I'd like to call Dr. Rose, please.
THE CLERK: Can you please raise your right hand?
Whereupon,
CARLOS D. ROSE
having been duly sworn, was called as a witness and was examined and testified as follows:
DIRECT EXAMINATION
BY MR. WISHARD:
Q Please state your full name.
A Carlos Daniel Rose, R-O-S-E. You can call me Rose.
Q Okay. Where do you work, sir?
A Say that --

Q Where do you work?
A I am the head of Pediatric Rheumatology at DuPont Children's Hospital, Thomas Jefferson University in Delaware.
Q How long have you been there, sir?
A I joined their group in 1989, and I became the head of the division in 1994.
Q Could you briefly summarize for the Special Master and the record your educational background?
A So I graduated medical school in North Buenos Aires, did my first rheumatology residency -- sorry, internal medical residency and then rheumatology training -- there in the city of Buenos Aires and moved to the States in 1987 where I took residency in pediatrics and then did my fellowship in pediatric rheumatology at Children's Hospital of Philadelphia, University of Pennsylvania.
I was then recruited to complete my training at Jefferson and then stayed on staff and then became the head of the division in '94. So I've been seeing children with rheumatic diseases. That's what I do all day every day except Mondays.
Q And today.
A And today.
Q What board certifications do you hold?

A I am certified in pediatrics and certified in pediatric rheumatology.
Q How many board certified pediatric rheumatologists are there in the United States?
A Two hundred and sixteen the last time we count. 216.
Q 216. Could you briefly describe your current position in pediatric rheumatology?
A So we have what is called a medium size center. We are three faculty that are full-time rheumatologists, and we have an American Board of Pediatrics approved training program where we train fellows.
So you asked me what I do. I am also a Professor of Pediatrics at Thomas Jefferson, and I spend I would say 50 percent of my time doing clinical work. I also chair the IRB committee for many years, so I do research ethics as part of my job. And I also have a research program on one of the monogenic autoinflammatory diseases called Blau syndrome. I run a registry and we do some collaboration with several labs working on a specific mutation that we're very interested called the NOD2 protein.
And I train fellows, residents, and I help them with their research. I have a connection within

the National Institute of Health where fellows do part of their basic research here at NIH, so we are in contact with them, including those who coined the term autoinflammatory disease. That's Dr. Kastner, who is here a few blocks away.

Q So 50 percent of your time is spent on clinical work?

A Uh-huh.

Q How would you divide up the other 50 percent of your time?

A Well, so I do research. I do ethics in research. I do teaching. Residents, fellows.

Q Okay.

A A typical pediatric hospital.

Q Obviously you have experience I think from your testimony in diagnosing and treating juveniles with pediatric juvenile onset JIA, correct?

A Absolutely. Yes.

Q Is that something you see and treat on a regular basis in your clinical practice?

A Yes, I do.

Q In terms of some of your research background, could you give the Special Master some information? I know we've filed your curriculum vitae, which I believe is Exhibit B in this case, but

just a summary of some of the research you've done in the area of systemic JIA.

A I have not done specific research on systemic JIA. I've done most of my work in the first part of my tenure has been lyme arthritis and most recently sarcoidosis or Blau syndrome, which is the one I referred before.

We collaborated with clinical trials and other efforts where juvenile rheumatoid arthritis patients are seen, and currently we have a research program that has been funded studying the function of fibroblasts from the synovial fluid of children with JIA with our collaborator, Dr. Bresser, and this is an ongoing study at the present time trying to anticipate a mechanism by looking at the cell behavior of the synovial fibroblasts if we can anticipate the outcome of the disease.

Q And have you gone through the process of obtaining grants in order to fund research in your role as a researcher at --

A Yes, but I wouldn't define myself as a person who spends a lot of time writing grants. I have had a few grants, currently have one from the University of Leuven in Belgium, and this is related to my study in Blau syndrome. That's B-L-A-U, Blau.

Q Have you published on juvenile idiopathic arthritis or the old term, juvenile rheumatoid arthritis?

A Yes, I have.

Q Have you been consulted or presented or done any research or publication in the field of vaccinations?

A I actually have one report of a case of transient arthritis following the lyme vaccine somewhere in my CV.

Q Have you been consulted in terms of vaccinations?

A By the HHS, yes.

Q Okay.

A Several times. Perhaps more than I want.

MR. WISHARD: At this time, sir, we would offer Dr. Rose as an expert in the field of pediatric rheumatology.

THE COURT: Ms. O'Dell, any voir dire questions on the qualifications?

MS. O'DELL: Just a few.

VOIR DIRE EXAMINATION

BY MS. O'DELL:

Q Dr. Rose, good afternoon.

A Hi.

Q Just a couple of questions for you or a few questions. Maybe more than a couple, but not too many.

A Uh-huh.

Q Are you an immunologist?

A No. I'm a rheumatologist.

Q Yes, sir. And have you done research on the role of proinflammatory cytokines in the relationship or in the development of SJIA?

A No.

Q Have you done any research on the Gardasil vaccine?

A No.

Q Any other HPV vaccine?

A No.

Q In terms of your testimony on behalf of the Department of Health and Human Services, Dr. Rose, I counted more than six times at least that are recorded in reported cases where you've given testimony.

A Okay.

Q But let me just ask the question. How many times have you given testimony on behalf of the Secretary of Health and Human Services in a vaccine case?

A Oh, my. I don't know. I mean, including

written and hearings or including just written testimonies?

Q Both written reports and hearings.

A I have been doing this, if I'm not wrong, since 1990, maybe '91. I can't remember exactly. There's an average of two, three or perhaps four cases a year.

Q Okay.

A I could be wrong. I mean, I really am just calculating, guesstimating.

Q I understand. So if it were 1991, that's 21 years ago.

A I can't believe this, but it is.

Q How time flies. Twenty-one years ago at four to five cases a year. Would an estimate be 80 to 100 times?

A I think that it may be a bit less, maybe around 60, but I don't -- I think 80's too much, so it could be around 60.

Q In any of the cases where you provided either an expert opinion via written report or testimony in the Vaccine Court, have you given testimony or opinion on behalf of a Petitioner?

A No.

Q Dr. Rose, what's your hourly rate for your

work in relation to the case?

A So we charge for the written report $300 an hour, and I don't recall how much for hearing, but I know it's higher.

Q Okay.

A It's higher here. I don't know how much more. I don't recall.

Q Okay. How many hours have you spent on the Koehn case?

A Altogether I think 15 so far, not counting today --

Q Okay.

A -- if I'm not wrong. I think it was 10 hours in the first report, I think five hours for the supplementary or eight. Eighteen. Fifteen. I don't recall.

MS. O'DELL: No further questions, Your Honor.

THE COURT: Dr. Rose, in the cases that you've been consulted on by HHS since 1990 or 1991, have you made any recommendations in favor of compensation?

THE WITNESS: One.

THE COURT: And what was the circumstance that you thought it was compensable?

THE WITNESS: I thought that they were married to the claim. There was a case of dermatomyositis and MMR vaccination, and it was within the right period of time and there were no associated additional triggers that were in the record that could have questioned the uniqueness of this attenuated virus vaccine and so I stated, if I'm not wrong, that it's equally likely that it isn't so I remained neutral towards the causality.

THE COURT: And that was MMR vaccine causing what type of condition?

THE WITNESS: Juvenile dermatomyositis.

THE COURT: Mr. Wishard, do you offer him in a particular field? I'm not sure if you did.

MR. WISHARD: Yes. Pediatric rheumatology.

THE COURT: Ms. O'Dell, do you object to that?

MS. O'DELL: No objection, Your Honor.

THE COURT: Okay. So we'll recognize you as an expert in the field of pediatric rheumatology.

THE WITNESS: Thank you.

DIRECT EXAMINATION RESUMED

BY MR. WISHARD:

Q Doctor, have you reviewed the exhibits filed in this case?

A Yes, I did.

Q And have you reviewed the two reports authored by Dr. McCabe and the literature filed in support of his opinions?

A Yes, I have.

Q And you've heard his testimony today, correct?

A Yes.

Q Based upon your review of this case, you provided two written opinion reports. Is that correct?

A Yes.

Q And those are marked as Exhibits A and F for the record. Let me ask you your opinion up front, and then I'll get into some of the details of your opinion. In your opinion, did the HPV vaccines received by Vanessia in 2008 more likely than not in your opinion cause her to develop systemic JIA?

A More likely than not they were unrelated events.

Q And in your mind, did the HPV vaccines play any role or provide any substantial contributing factor to her development of systemic JIA?

A No.

Q Let me ask you just briefly, if you could,

just give a brief summary of Vanessia's clinical history from your understanding of the records.

A So what I stated here in my record, in my report, apparently healthy childhood and adolescence. 2-18-08 gets the first HPV vaccine, and then on June 24 she was evaluated for a skin rash that commonly is interpreted initially as urticaria rash. She was not treated just with antihistamines. She was treated with antihistamines and corticosteroids, which are a more powerful, antihives kind of treatment.

When the corticosteroids were discontinued, because that was the plan of the treatment, the patient showed a diverse manifestation of systemic JIA. And I want to point out that that's similar to the event that happened after the third vaccination where she both times upon withdrawing of the steroids she showed the symptoms of the disease.

Q And no doubt in your mind that she has systemic JIA?

A No doubt.

Q And before I further delve into your opinions, if you could just briefly discuss your understanding from a medical standpoint of systemic JIA in terms of is it --

A And you want to go home tomorrow?

Q What's that?

A Do you want to go home today?

Q I said briefly.

A Yes.

Q Let me ask you some pointed questions. Is it your understanding that it's an autoinflammatory disease?

A Yes, it is.

Q Does it have an autoimmune component?

A No, serologically at least.

Q And why do you say that?

A Well, Dr. Kastner, when he started to use the term autoinflammatory diseases in the '80s based on his work on familial Mediterranean fever, he made the distinction between the two fields, the autoinflammatory versus the autoimmune, by the presence in the serum of anti -- including antinuclear antibodies and rheumative factors.

So that was a clinical definition that worked very well because, thanks to that, we've discovered a lot of genes since then that are very relevant, but his definition was clinical and based on the absence of antibodies to nucleus or to the rheumative factor in the serum of these patients.

Q How is systemic JIA treated in general?

A So normally a patient with systemic JIA receives first a short course of anti-inflammatories. We try with anti-inflammatories first. Sometimes we get a response. Rarely we do. And then we initiate corticosteroids, Methotrexate, for the majority. This is the standard of care these days. We push the dose up to the maximum tolerable, and if we don't get a response within four or five weeks we move to the biologicals. I rarely use it to intercept. Like in this case we used a very similar one called Remicade, which we believe is more powerful to control systemic JIA.

Then we use Anakinra, which is the interleukin-1 receptor antagonist. It's actually becoming the mainstay of treatment in other parts of the country. We've got all these ways that we use here on the east coast. Some patients are starting on Anakinra at diagnosis.

And then we use Tocilizumab for those who fail Anakinra because we assume that there are subsets within systemic JIA where they're more IL-1 dependent, they're more IL-6 dependent, and there are others -- not many -- that are predominantly TNF, and the proof, the only proof of that, is that they respond to a specific biological therapy.

We use anti-TNF first, although that may change soon, because it's the first ones that we've been using, the first to be approved, so we continue with that sequence. But that may change soon.

Q And in terms of Vanessia's treatment, she received anti-inflammatories. Is that correct?

A Uh-huh.

Q And she also received several courses of corticosteroids?

A Uh-huh.

Q You mentioned I think she received Enbrel. How does that fit into the picture in terms of what is that?

A So Enbrel is a decoy of the receptor for the TNF alpha, and by binding the -- and it's not just a TNF receptor. It's a TNF attached to an immunoglobulin protein. And it happens that this, which is a recombinant product, has more affinity for TNF than the actual natural receptor, so in a way by binding it, it impedes its binding to its natural receptor.

Remicade, which is also an anti TNF, is a monoclonal antibody to TNF instead of a decoy of the receptor, but both work on the same target.

Q Is Enbrel effective immediately upon initial

treatment?

A So the clinical trials that led to the approval of the drug conducted by the Pediatric Rheumatology Collaborative Study Group of which I was a member of the executive committee, the first trial that was completed in the year 2000, the average duration to the effect was about four weeks.

But there were patients who required up to three months in order for them to achieve the outcome measure, which was an improvement by 30 percent of what are called the core criteria, which are a complex of joint count, sedimentation rate, et cetera, which we create a score, and a 30 percent improvement of that was considered a positive outcome measured compared to placebo, and that's what took, three months the outside range, for a response to treatment.

Q And in terms of the clinical history for Vanessia, is there anything in Vanessia's history which would indicate to you that she has some type of atypical pattern of systemic JIA?

A No.

Q Okay. I want to focus a little bit on your reports, which are Exhibit A and Exhibit F. You mention in your reports, first Exhibit A on page 2, about the role of infections in arthritis, and then

you went into some other detail on Exhibit F, page 2, responding to several citations from Dr. McCabe. Could you just generally explain your thoughts and why you framed the issue the way you did in your initial report, Exhibit A, regarding the role of the natural infection, HPV infection, and arthritis?

A If you could, on page 2 what paragraph of my report?

Q Sure. Exhibit A, which is your first report.

A Uh-huh.

Q Page 2 at the bottom when you have framed the questions 1, 2, 3.

A I see. So this is based on the way I approach these cases as a clinician. I'm not a basic researcher, so the way I look at the record and I look for possible triggers of the disease. And after that I think of what is happening in the real world with arthritis and infections.

So in pediatrics, unlike in adults, postinfectious arthritis is a common situation. For example, lyme disease is the most common cause of arthritis where I practice, followed by juvenile rheumatoid arthritis, so if, in my view, if a known infectious agent is capable of producing arthritis,

the vaccine to which we are trying to prevent the infection from, it's more likely to mimic that phenomenon.

And so in the case of human papillomavirus, I haven't seen, as I think was recognized already, any case of any form of rheumatic disorder in association with the natural infection, either systemic JIA or any other. Is that what you were asking me?

Q That was what I was asking you. Thank you. And in terms of looking at the top of Exhibit A, your report, page 2, you talked a little bit about the IL-1 and IL-6 networks. How do they relate, in your understanding, to SJIA?

A So the work on IL-6 has been mainly coming from Dr. DeBenedetti, who has been referenced previously, who had been working on IL-6 for many, many years. And so the reason IL-6 was looked at is because many of the manifestations of the disease sound like IL-6 activation, including the acute phase reactants, the high fevers, et cetera.

Now, in very early studies it has been shown that the production of IL-6 in this basis is extraordinary and that the peaks of fever, which this disease is characterized by two spikes of temperatures today called hectic fever -- it's a very particular

pattern of fever -- are preceded in hours by a peak in the IL-6 level in the serum. So you can pretty much follow the IL-6 level in the serum and you can follow with that the temperature.

That's why it was always thought it was an important if not cause, important determinant of the symptoms of the disease, the manifestations, and with that came the whole idea of IL-6 being central.

IL-1, I think it was always thought that Dr. Vitarello, who was the first one who described the IL-1 cytokine, was initially a cytokine that we related to a doldrom (phonetic) arthritis and its ability to produce erosions in the hands. It was when the autoinflammatory diseases came back, and particularly I don't know if you're familiar with the mutations and CAPS, Nomead (phonetic) and Michael Wilson, series of monogenic disorders which are characterized by excessive upregulation of IL-1.

It was at that time that the IL-6 in systemic JIA became again looked at, and we have an inhibitor that was approved for RA, Anakinra, and so it was started to be used in systemics and the results are extraordinary. So I think in my view as a clinician the role of IL-1 and the role of IL-6 in this disease are mainly proved by the fact that by

giving them specifically we control the disease in a good percentage of patients, but not in all.

Q I missed one point in the issue of infection. I want to jump back. If you could look at Exhibit F, page 2, which was a responsive report to Dr. McCabe's questions that the Special Master had. You referred to three citations, which I believe were the citations referred to by Dr. McCabe, Exhibits 12, 13 and 15. You state that the three citations are statements of hypothesis generation.

A Uh-huh.

Q Can you explain what you mean there?

A Yes. I don't have them in my mind, but what I mean by that is that these are questions presented to the research community in order to plan the either biological or epidemiological studies to prove or disprove those hypotheses.

I would say pretty much what was said before. It's just kind of they don't report anything. They just simply report there is enough background there to go ahead and test this. That's what I would call hypothesis generation.

Q Okay. And you state later that the same author cited by Dr. McCabe recognized that none of these studies were able to isolate any specific

infection or vaccinations.

A Correct.

Q Okay. Getting back to your first report, which is Exhibit A, I want to skip ahead to one point that Dr. McCabe made. On page 7 of that report there was an issue concerning your reference to IL-8 --

A Uh-huh.

Q -- where it says Some Interesting Findings in the Context of Vanessia's Disease. Would you like to explain --

A Yes.

Q -- that paragraph there in terms of --

A Yes. Sure. So this is an error. The reason for this error was that I had read Mellins's paper way before, so I thought I recalled that. It so happens too that I talk to Alexi Granquist, who is one of the authors, quite frequently, and we were talking about IL-8 in other circumstances so at the time I wrote this I got the two confused basically. I know that they're very different. One is a chemokine and the other one is an IL-1 related cytokine.

Q Does this error in any way impact your opinions of the case today?

A Not at all.

Q The Petitioner's theory here that the HPV

vaccine caused a proinflammatory cytokine response, which then caused or can cause systemic JIA. Is that something that's discussed by the pediatric rheumatology community at all?

A No. What is mostly discussed is the safety of these vaccines in patients with systemic JIA.

Q Is that theory something that I guess if we had all the money in the world could be looked at in terms of whether or not the vaccine can cause systemic JIA?

A Yes. I think I would put it that way. Maybe we don't need that much money because there are two mouse models currently not exactly on systemic JIA, but they're on HLH, which is the actual name of macrophage activation system. One is being tested in the University of Leuven in Belgium, and the other one is at Penn.

And so at least when we start injecting those mice we'll see what happens. It will give us clues if there's anything unusual about this particular vaccine compared to other vaccines. Maybe it will justify or make the grant more appealing to granting if there's any background on that.

So I would start by doing something, a really simple pilot on looking at this before I go to

the very expensive -- as for the value of the research question, if I am the one that is giving you the funding I would say why would you do that? Why not test other hypotheses first because this seems to be very unlikely?

Q Dr. McCabe testified and I think you put in your report that there's no epidemiological data to suggest a correlation between the HPV vaccine and systemic JIA or chronic arthritis in general.

A Uh-huh.

Q Is that your opinion, sir?

A Yes, it is.

Q In your looking through the literature, did you even see any case reports regarding systemic JIA?

A No, I haven't.

Q And my understanding in terms of the level of investigation, is it true or is it my understanding -- what's your understanding in terms of case reports in terms of the context of research and looking into an issue?

A I'm sorry. Looking at vaccine causality or in general?

Q Let's talk about vaccine causality.

A So a case report that is unprompted, that you have a situation where we have one clinical

manifestation following a vaccine, such as this is a case report. I mean, the one that we are discussing today. We are trying to attribute causality to events that occur in the same person at a given time. So this could be a case report. If I am on the editorial board of that journal I would not accept it. That's how I think of case reports of this type.

Q Dr. McCabe discussed as well the fact that there was the lack of any case controlled studies focused on this issue. Is that your understanding as well?

A Yes.

Q And how about animal models focusing on this issue?

A Well, as I mentioned, there's not one for systemic JIA. There are several models for arthritis and this macrophage activation syndrome model.

Q There's been some discussion about the fact that the issue of vaccine-induced JIA has been looked at with the MMR vaccine and the meningococcal vaccine --

A Uh-huh.

Q -- and that there were several articles that were filed in this case.

A Yes.

Q Do you have any opinions in terms of their impact on your opinions here in this case dealing with the HPV vaccine?

A Yes. So I think the situation where they looked at the safety of those vaccines in children with the disease goes a little bit to answer that discussion that was in the previous testimony as in a patient who has the disease will be a good candidate to see what happens when you vaccinate them.

So of course we don't have anything with HPV, but these two vaccines seem to have a wonderful record of safety in patients with JIA for both, and we do clinically recommend those vaccines. We recommend all the vaccines in all patients except live viral vaccines who are on Methotrexate or Enbrel or have systemic JIA.

Q And just for the record, what I was specifically referring to was Exhibit 43 regarding the MMR vaccine and looking at juvenile idiopathic arthritis, which I think you have a copy of.

A Yes. Correct. And this is what I was saying, that this is Dr. Wilfred, who is the senior author, belongs to the same group as Dr. Prakken that was mentioned several times -- this is University of Utrecht. And what they did was exactly that, look at

the safety of MMR vaccine in JIA, and they found nothing.

Q I want to skip to Exhibit 26, the first Pinto article.

A Yes.

Q Do you have that?

A Okay. Wait. Let me organize my papers.

Q No problem.

A Yes. So we are talking about 26, Pinto when she was the first author.

Q Correct.

A Yes.

Q The 2005 Pinto article, Exhibit 26.

A Uh-huh.

Q And flipping to page 4 of that, that's the table that was up on the screen earlier. In your review of this article, does it have any importance in your opinions today and do you have any comments about it?

A Yes, I think so. I think it's a great work. This is Bethesda, I think. This is NIH. So I think it has been clear by Dr. McCabe the purpose of this, they were looking for a pattern of vaccine response in terms of using in this case the Luminex technology, which looks at many cytokines at the same time. And I

think the focus of the discussion today was on vaccinees versus placebo whose ex vivo -- that means their white cells are exposed to the antigens of the vaccine -- and then you look at what they release and take the supernatant and measure it. That's what pretty much this is.

But I wanted to move you to the other side of that table, which is the first column where they look at media only. And media only means that these cells are now being stimulated by the same protein to which these people have been immunized before, so this is how they are before and after vaccination, how the cells behave when you leave them alone.

And because for me the crucial question here is not that if the pattern of cytokine upregulation by the vaccine is similar to the pattern of upregulation as you see in systemic JIA, but if it is a sustained pattern. Can you by injecting an individual with a vaccine that upregulates the cytokines, can this persist because that's what I see in the clinic?

These patients are constantly with elevated levels of, assuming, IL-6, IL-1, because we need to keep the medications going. We stop the medication and they flare, as you can see in this case and in any

other that has not gone into remission yet.

So in the first column you can see that after vaccination at times zero, two and seven particularly I was pointed to TNF alpha because TNF alpha is being inhibited. In this particular case it's working, so I assume that TNF is relevant for Vanessia. And I don't see any change, spontaneous release of TNF, after two vaccinations.

Actually you see if you look at the columns vertically you can see that for almost no cytokine there's a spontaneous release of cytokines that is different at time zero compared to time two and time seven, and to me that's very suggestive that the response that this vaccine elicited in these normal people has not been sustained.

Q What about on IL-6 and IL-1?

A Well, you see IL-6 is for the median 25.9, 23.8 and 21.4 in the zero, so they have as much before as they have after, and IL-1 is four, 3.6 and 2.5. It seems to be if anything, I think this is all nonsignificant going down, so it's not maintained.

Q Anything else about Exhibit 26, the Pinto article, which you think is significant in terms of the issues here today? And I should say other than what you discussed in your report on pages 6 and 7

except for the one error referring to IL-18.

A No. No, no. I think I covered this because I thought it was a very interesting paper. No. I think that -- oh, the only other thing that I want to point out is that if you -- and I'm not an immunologist. I couldn't be even starting to design research like that. I'm just interpreting as a clinician what I read.

If I have in my pallet primed cells, primed by the immunization, the more I add the same protein the more explosive the response will be, as is shown in the other study with proliferation. I think that was cited before -- I wish I could remember -- when they look at the proliferative response that goes up as you vaccinate them. That's expected because you have a more sensitized set of white cells. You tickle them with the same thing you vaccinated a person with. It would produce cytokines in significant amount.

Q If we can move on now to Exhibit 28, which is the second Pinto and Garcia-Pineres article.

A Uh-huh.

Q And this one you didn't specifically talk about in your reports. Anything based on your review of this article and the testimony today that would contribute to the issues that we're dealing with in

this case, in your opinion?

A No. This is the newer article where Pinto is the senior. Is that right?

Q Yes. 2007.

A 2007. So they expanded from 15 to 22 cytokines. More of them became available, and for a bunch of them that are relevant to us -- TNF, IL-1, IL-6, IL-8 -- which are what they call the inflammatory cytokines of which there was no correlation in the values. They did good statistical work on this. And then I don't think that these two studies deferred too much in showing. It's pretty much the same idea of putting them with the antigens and seeing what the response is, but again values on the media. When they're unstimulated, they don't seem to have an abnormal behavior.

Q If we could go next to Exhibit 30.

THE COURT: You said when they're not stimulated they don't seem to have an abnormal behavior?

THE WITNESS: Correct. What I'm saying, so you take the white cells of the vaccinated person where there's in theory memory to that vaccine and you rechallenge them with the antigen in vitro then they produce cytokines in excess and more as you have them

more vaccinated. Well, if you expose them to the media alone they're not releasing anything, meaning these individuals who were vaccinated at the time they were a sample, there's nothing sustained spontaneously, which I find expected.

In general, you don't want people that you vaccinate to remain inflamed for the rest of their life, but that's my main criticism of the theory that by activating or by making these cytokines be released at a point, A, it will become the disease. That is why I'm making the point on this.

BY MR. WISHARD:

Q Let's go next to Exhibit 30, which is the Evans article which was discussed by Dr. McCabe.

A Yes.

Q Again, you didn't comment on this report specifically in your two filed expert reports --

A No.

Q -- but based upon your review of this article and the testimony you've heard today do you think that it assists us in terms of any of the issues in the case?

A Yes. This is the article I was looking for when I was looking for the expansion of the T cells, and this is the article that shows that these T cells

are really more proliferated and have proliferated in the vaccination, and I think that that's why they produce more cytokines when you stimulate them.

Q And this is Exhibit 30, Evans?

A Uh-huh.

Q Anything else about Evans?

A Actually, no.

Q Exhibit 32. This is the Emeny article.

A Uh-huh.

Q I'm not sure if this one was discussed today or if it was discussed in Dr. McCabe's report, but have you had a chance to review this article as well, sir?

A Yes, I did.

Q And does this article add to any of the issues? Let me back up. You haven't had a chance to comment on this article. Is that correct?

A Yes. I was actually reviewing this article. I think unless there's a specific question that you have about it, I don't have anything to add.

Q Okay. Very good. We can move on then to Exhibit 34. This is the Chao article which was discussed today.

A 34.

Q If you don't have a copy, I can give you a

copy.

A Hmm?

Q If you don't have a copy, I can give you a copy, sir.

A Yes. I thought I did, but I don't have Chao. It must be over there.

(Pause.)

A Okay.

Q And again, this is an article I don't think you commented on in your two reports, but have you had a chance to review this article?

A Yes, I did.

Q And do you have any comments or thoughts in terms of its impact on the issues of this case?

A This is a study that, if I'm not wrong, shows nothing specific in terms of epidemiologic data on systemic JIA.

Q Anything else?

A No.

Q And I want to just briefly go through the three articles you cited in your reports, the first one being Exhibit C, which is the DeBenedetti article.

A Uh-huh.

Q Why did you cite to that, and why is it important in this case?

A I think that was in support of the role of IL-6 in JIA.

Q Okay. Anything else, sir, other than what you referred to?

A No. This is a review. It's a chapter article.

Q Okay.

A Excellent, but just a chapter.

Q The next one is Exhibit D, which is the Mellins article, which was also cited by Petitioners in this case.

A Uh-huh.

Q Again, anything in here that hasn't been discussed that you want to raise?

A One of the best review articles in systemic JIA that we have at this point. It has several clues as to what could be the mechanism of systemic JIA, and they make this show about the similarities with macrophage activation syndrome. The sense is that there could be more than one gene possible, but they haven't ruled out that this disease is monogenic.

Q Anything else, sir, on that?

A No, not beyond what I wrote.

Q Okay. And the final one, which there was some questions of Dr. McCabe from the Special Master.

This is Exhibit E. This is the Verstraeten article.

A Uh-huh.

Q Anything in this article that you want to add in terms of the issues in this case?

A So I think this is the closest that we can get to an epidemiologic study. This is a study of about 60,000 individuals. The incidence, meaning the annual incidence of systemic JIA, is about .8 per 100,000. This covered two years of followup. I have to agree with Dr. McCabe. When you have zero there's not much you can say, but if this vaccine was doing something I would have expected at least one or two cases. It's not an enormous sample. It's not a millions of people sample, but it's pretty reasonable. If this was a significant trigger I would expect to see one or two cases of systemic JIA in the vaccinees.

Q Now, in your review of Vanessia's treatment records did you see in there any belief by any of her treating physicians that they thought her systemic JIA stemmed from her HPV vaccinations?

A No.

Q And in terms of my understanding of the timeline here is that after the second HPV vaccine she had an onset of symptoms, and then she received a third HPV vaccine.

A Yes.
Q Is that correct? And in terms of standard practice, is that something that for your patients who have systemic JIA do you have any recommendations in terms of whether or not they should get the HPV vaccine?
A Absolutely. We recommend HPV vaccine for several reasons because first it's a recombinant vaccine so we think it's safe in the immune-suppressed population. Second, the drugs that we use for these patients, they are more prone to develop cancer with HPV, so we do recommend it.
Q And in terms of Vanessia's treatment records after her third HPV vaccine, is there anything you saw in Dr. McCurdy's records from September 3, 2008, which would be Exhibit 5, page 45 and 46, which would be the next rheumatology visit, which would indicate that Vanessia had any type of reaction to --
A A flare. Yes. So he describes a flare he attributes to the discontinuation of the corticosteroids, which is reminiscent of what happened the first time.
Q And did she have in addition to when you say the flare, do you mean the rash that reoccurred?
A The rash and increased joint pain. A

typical flare in a systemic patient.
Q And then in terms of Dr. McCurdy's next visit, December 5 of 2008, which is Exhibit 5, page 43, was there any indication there that this flare continued once she was back on the medication?
A No. It looks like she was well controlled as expected.
MR. WISHARD: Special Master, those are all the questions I have. Thank you.
THE COURT: Ms. O'Dell, are you ready to jump right in, or do you need a break?
MS. O'DELL: You know, I'd love a five-minute break if you could accommodate that, but if you want me to jump right in I certainly will.
THE COURT: We can accommodate a five-minute break. Sure.
MS. O'DELL: Great. Thank you.
THE COURT: Why don't we go off the record?
(Whereupon, a short recess was taken.)
THE COURT: On the record. Ms. O'Dell, whenever you're ready.
MS. O'DELL: Thank you, Your Honor.
CROSS-EXAMINATION
BY MS. O'DELL:
Q Dr. Rose, I have a few questions for you

today. Let me turn your attention first to this discussion we've had about SJIA being an autoinflammatory disease versus an autoimmune disease.
There's been quite a discussion about that in reports and during the development of this case. Would you agree with Dr. McCabe that SJIA is an autoinflammation process, an autoinflammatory process?
A Yes.
Q You would. And is that always the case that JIA is an autoinflammatory process?
A Yes.
Q Would it ever be true that JIA is an autoimmune disease?
A The subset characterized by positive rheumative factor or the subset characterized by antinuclear antibodies can be considered autoimmune diseases.
Q Okay. And let me ask you this. On page 4 of your report, your initial report, you discuss at the bottom, you're commenting on Dr. McCabe's initial report. You say he lumps together autoimmune diseases as a general theory of causation. I think that has been clarified at this point. Then you say it's misleading since systemic JIA is not an autoimmune disease. And so I want to ask you again. Outside the

context of litigation have you taken the position that JIA is an autoimmune disease?
A Let me put myself in the discussion with parents, which is where I use most of my lay terms. I don't think that this discussion is that relevant in the world of research or academic world. We are beyond this discussion for many years. But when I explain to a parent -- let's not talk about systemics. Could I take one of the other examples like the oligoarticular JIA, which has more autoimmune features? Would that be acceptable?
Q Sure.
A So I see a two-year-old with a swollen knee and a post event antinuclear antibody, and they have a 20 percent chance of developing inflammation in the eye, something called uveitis. So I explain to them that the uveal tract of the eye is a place where the immune system normally doesn't mess around too much because of the importance of those tissues to remain crystal clear, and it's very likely that the uveitis of juvenile idiopathic arthritis ANA positive has autoimmune features in the eye.
As for the mechanism by which the point is inflamed, we don't know that there are actually antibodies to or T cells to joints. There is some

evidence that the fibroblasts of the synovial membrane are activated and not necessarily responding to autoantigens. So if one uses a very strict criteria for autoimmunity then you have to be very careful.

When I try to explain to a parent what autoimmunity is I use clinical facts, the presence of certain elements of the clinical picture, to explain the disease. Perhaps the most clear of all is myasthenia gravis where you have an antibody to a receptor and you have muscle weakness as a consequence or you have an antibody to collagen-4 and you have another type of renal disease.

So those are the clear autoimmune where there is a T cell or is an antibody that binds part of your tissues and produces clear-cut pathway of disease. Then you have the other extreme where there is no evidence of autoimmunity in the serum. Examples of those are diseases for which we have a mutation. Example, familial Mediterranean fever. Clearly autoinflammatory.

And between you have features of both. You will have diseases where the autoimmune mechanism is important, but the manifestations are predominantly inflammatory and vice versa. For example, in myasthenia you have 100 percent autoimmunity. There's

no one cell that is inflamed there. You have the receptor to the binder, the acetylcholine, and boom, you get weak. And there's no inflammation there. So you have examples of pure autoimmunity, examples of pure autoinflammation and a lot of in betweens. I'm not the first to say that, by the way.

Q You've been talking in terms of a clinical setting. Let's take it out of that setting in terms of the scientific literature. And you would expect what's been written in the scientific paper to be precise, true?

A Yes. Certainly.

Q And so let me ask you, Dr. Rose. Were you an author on a publication in 2010 in Arthritis Rheumatology?

A Arthritis & Rheumatism, yes.

Q Rheumatism. Excuse me.

A In 2010?

Q 2010.

A Which one was that?

Q In the introduction of the paper it says, "Juvenile idiopathic arthritis is a childhood onset autoimmune disorder."

A Yes. Could you tell me the title of that, the title of that paper?

Q Yes. The Susceptibility Loci Juvenile Idiopathic Arthritis Shares With Other Autoimmune Diseases.

A This is actually a study done on polyarticulars and ANA positive oligoarticulars and so we did not argue with Sue Thompson, who is the first author of that paper, in calling that autoimmune because there were no systemics.

Q Okay.

A So as I said --

Q So you may disagree with her outcome?

A If we're talking about systemics, that word would not have gone through. You need to understand that in rheumatology we try to classify the patients very precisely because treatments are different and outcomes are different.

Q All right. So you may have disagreed with Dr. Thompson, but you're still an author on the paper, true?

A Yeah. I would have disagreed if there were systemics in the population, but there weren't.

Q Okay. Let me ask you, Dr. Rose, about the Verstraeten article that you cited and I believe you had as Exhibit E.

A Yes.

Q Isn't it true, Dr. Rose, that the Verstraeten article did not involve the Gardasil vaccine?

A That's correct.

Q And that in fact it was a study involving Cervarix, true?

A Yes.

Q And Cervarix has a different adjuvant than Gardasil, true?

A Yes, as far as I know. I'm not an expert in vaccine, but I take your word for it and Dr. McCabe's.

Q But based on the study and the paper --

A Yes.

Q Based on, excuse me, the text of the paper --

A Exactly.

Q -- the adjuvant is not the same as the adjuvant in Gardasil, true?

A Correct.

Q And the adjuvant in Gardasil is an aluminum-based vaccine?

A Yes, as far as I know.

Q And that is not the case with Cervarix, true?

A As far as I know, it is not.

Q And let me just talk to you just a few minutes, a few more minutes, about this paper. You said a while ago, and I want to make sure that I've said this correctly, but you said in the Verstraeten paper that there were no cases of SJIC (sic), true?
A SJIA.
Q Excuse me. SJIA.
A Uh-huh.
Q There were no --
A Cases.
Q -- cases seen, and in fact you testified a few minutes ago that if it was a trigger that you would have expected to see one or two cases. Did I restate your testimony correctly?
A Yes. So what I'm saying is given the prevalence of systemic JIA in the population, I agree that we're still below the number of patients that you would expect to see one case, but I wouldn't be surprised if I saw one or two, at least I saw one or two. Do you follow me what I'm saying? Statistically the confidence interval could have included zero of course.
Q Right. But, Dr. Rose, isn't it also true that you would never see a case of SJIA if it was not an end point in the study design? Isn't that true?

A If I do the study or somebody else does the study?
Q I'm talking about the Verstraeten paper --
A Oh, these guys? Oh.
Q -- and the study that they performed and that's been published and which you cite. That's what I'm referring to.
A Sure.
Q And you stated that there were no cases of SJIA.
A Yes. That's correct.
Q But isn't it true that SJIA was not an end point in the Verstraeten study?
A Well, you know this is a collection of studies so I really don't know the inclusion criteria of all the studies of what these were based upon. This is a -- you understand? So I did not review the individual studies, but I have to say that normally juvenile rheumatoid arthritis usually in old terminology could be an end point.
Q Could be, but it's not in this study, though, is it, Dr. Rose?
A Recall this is not a study. This is a collection of studies.
Q Well, this publication.

A Yes.
Q So SJIA is not seen in the Verstraeten publication?
A Let me answer that question by saying I don't know what the inclusion criteria of the original studies were. If you ask me an assumption, it could be that it is not listed because it didn't happen and it's not listed because they didn't look for it.
Q Well, let me direct you to Table 2 on page 6633.
A Uh-huh.
Q And Table 2 lists the adverse events of potential autoimmune etiology used to search the safety databases.
A Uh-huh.
Q And in that table is there a mention of systemic JIA?
A No.
Q Okay. And if you'll turn over to Table 3? Is there a mention of systemic JIA?
A No.
Q And so when you testified that there were no cases of systemic JIA, in part isn't that true because systemic JIA was not one of the end points they were looking for when they searched the databases? Isn't

that true?
A I don't know that I know enough of the paper to answer that question, but I cannot. I'm neutral to that.
Q Okay. Let me ask you this, Dr. Rose.
A Yes?
Q What is your view of the background rate of SJIA?
A .3 to .8 per 100,000.
Q .3?
A To .8.
Q .8.
A Per 100,000. So one in 100,000. You said prevalence or incidence?
Q I said incident rate.
A Incidence? Again?
Q Yes.
A So yearly new cases.
Q Correct.
A New cases seen in a year. In northern European countries and in the States, it's somewhere, to make it simple, between .5 and one per 100,000. It's .3 to .8.
Q I want to make sure I understand you.
A Yes.

Q Between .5 and one per 100,000 is the incident rate as you understand it for systemic JIA?

A In the northern European countries and in the U.S.

Q Yes, sir. And so with that low of a background rate, how large of an epidemiological study would you have to have in order to test in a meaningfully statistical way the relationship between SJIA and the introduction of Gardasil?

A To answer that question you need to know what's the likelihood of the vaccine producing the disease. If the vaccine is the real cause you can see cases. So when you do a power calculation on your sample site you need to anticipate somehow what do you expect to see in the population. If you expect to see zero in the population there's no trillions of patients that will be enough. So if you expect to see that for every -- it all depends on how strong you think the course is to figure out the number of patients that you need.

Q But isn't it true, sir, that with that low a background rate that you could have a study upwards of 800,000 patients and you would have to have a study of upwards of 800,000 patients in order for it to be adequately powered to study SJIA as an --

A I don't want to say that. I really need a calculator or somebody to help me to really calculate it. If you are basing it on the population -- in other words, the control group will be about one in 100,000 -- that's where you're basing it. In other words, the unvaccinated people, you need 100,000 to see one. You may need 100,000 to see more than one if the vaccine is causal. So maybe you need 100,000. I don't really know the answer.

Q Let me ask you --

A At least you need 100,000.

Q -- Dr. Rose, to turn to Exhibit 34, the Chao article that you testified about a few minutes ago. And in regard --

MR. WISHARD: Excuse me, counsel. I may have to give him that.

THE WITNESS: I don't think I have that one.

MR. WISHARD: I think that was the one you didn't have.

THE WITNESS: That I don't have.

MS. O'DELL: Sure.

MR. WISHARD: If you'll indulge me for a second? I apologize.

THE WITNESS: That's the one you gave me and then took.

MR. WISHARD: Yes.

THE WITNESS: Okay. Yes. I have it in front of me.

BY MS. O'DELL:

Q You testified in regard to this article, Exhibit 34, the Chao article, that there were no cases of SJIA reported in this article, true?

A I have to look at my report to say that. Dr. McCabe gave us a lot of articles to comment on, so I don't remember if I said that about this.

Q You're welcome to look at your report, sir, but I'm talking about what you testified to when Mr. Wishard was asking you questions just a few minutes ago.

A Uh-huh. Okay.

Q So you're welcome to look at your report, and I'm glad to give you a moment to do that, but --

A No, no. I understand. So you were not referring to what I said in my report, but you were referring to what I said before?

Q Yes.

A Thank you.

Q Just a few minutes ago.

A Okay.

Q And in regard to SJIA, sir, you said there

were no reports of SJIA in this publication, and in doing so you suggested that there were no events, no SJIA events. But I'm asking you, and I wanted you to look at the article and tell us if systemic juvenile idiopathic arthritis was an end point in this study?

A I don't remember the inclusion criteria nor the -- let me see. They list the autoimmune conditions of interest on page 194 at the bottom and in Point I or 1, rheumatologic autoimmune disorders including IPP, autoimmune hemolytic anemia, systemic lupus, rheumatoid arthritis and juvenile rheumatoid arthritis. It's not my fault that they use the old terminology. That's what they use. We don't use JRA anymore. That's the term, but it should capture the systemics.

Q It's 2011, sir. It's not an old publication. What makes you assume --

A Yes, but the criteria changed 10 years ago.

Q What makes you assume that they weren't using --

A Because JRA is not used anymore as a term.

Q But there is nothing in this to suggest, because we're talking about in this particular study autoimmune conditions, true?

A Yes. That's what the title says.

Q That's what the title says.
A Yes.
Q And we've I think concluded that systemic JIA is an autoinflammatory disease, true?
A Yes.
Q And so what's also true is that the Chao article does not comment at all on systemic JIA, does it?
A It doesn't show any cases. Correct.
Q Because it didn't study systemic JIA, did it?
A Well, they tell you they are not even talking about JIA. They are talking about JRA. So how much these people know about rheumatology I don't know. I did not write the article.
Q I understand.
A So if these individuals are using the 1980 criteria for nomenclature it's not my fault.
Q Well, but you'd have to agree with me this article, the Chao article, does not discuss systemic JIA, wouldn't you, sir?
A Well, if you -- let me make this clear. If we were before the ILAR reclassification in 1992 we would be calling systemic JRA -- that's what we'll call it -- oligoarticular JRA -- we would be using the

R.
Now, these individuals wrote this paper in 2011, and they are using the nomenclature that was abandoned in 1992 or 1993, but if you think that these people are in the past using the old nomenclature, those JRA patients should include systemics in them.
Q But there's no evidence that you're aware of that suggests that in 2011 --
A Absolutely not. I don't know how far they went. Yes.
Q -- that individuals from Kaiser Permanente and Merck Research Laboratories and others are in the past, is there?
A For the terminology of juvenile idiopathic arthritis, yes.
THE COURT: Wait. I think that was a misconnect between a question and an answer because you had asked that there is no evidence that they're in the past, and Dr. Rose said yes. But you had said that there was no evidence, but I think he's saying that there is evidence. That's the way I understood that because you asked your question phrased negative.
MS. O'DELL: Okay, Your Honor. But he's suggesting that the authors of this paper somehow are using nomenclature from 1992 in a publication in 2011

and somehow that suggests that systemic JIA was included as an end point in this article.
THE COURT: I think that's fair because the nomenclature of JRA in 1992, the old nomenclature did include SJIA, so that's right. I mean, I haven't heard anything that said that that's wrong. I think the other point that you made, Ms. O'Dell was that the article is looking for autoimmune conditions, but SJIA is not an autoimmune condition so that makes some doubt to me whether they were looking for SJIA in this or whether this study would have captured SJIA because it's autoinflammatory, not autoimmune.
But I think their use of the term JRA seems like that used to be the broad term that's been replaced now by JIA, but SJIA is part of JIA, formerly known as JRA. It certainly would have been more helpful if there was something specifically saying systemic juvenile idiopathic arthritis, but we don't know. We only have what we have.
MS. O'DELL: Right, Your Honor. And really the point of my questioning Dr. Rose about this is that he made some very specific comments about SJIA in relation to this paper, and I'm just pointing out that you could make some assumptions about what was included in JRA obviously, but that there's nothing in

the paper really that reflects that understanding or that assumption.
THE COURT: There's nothing in this paper, but there is a basic understanding that the old term of JRA included SJIA.
MS. O'DELL: I understand.
BY MS. O'DELL:
Q Okay, Dr. Rose. Let's turn to page 3 and 4 of your report. On the bottom of page 3 of your initial report you turn our attention to a table from the Gardasil label --
A Yes.
Q -- and you state that the table shows that there have been no reports of SJIA. Sir, let's look at the table for just a few moments. You see under the Gardasil column you have N number as 10,706 under Gardasil, 9,412 under AHS Control or Saline. Do you see that?
A Yes, I do.
Q And what's your understanding of where these numbers originate from?
A This is from the label, from the vaccine label, and they represent spontaneous report in the posttrial.
Q When you say posttrial, are you talking

about the numbers that were reported in the clinical trails in relation to Gardasil?

A Yes.

Q Okay.

A Yeah. That's my understanding. I've done this a year ago, so I do think that this is the table below obtained from the vaccine label are gathered by the sponsor via self-reporting mechanism after the trial, so that means posttrial. This is a followup of the patients who were in the trial. This is on page 3, bottom left paragraph.

Q Yes. So that's the point. These patients were in a clinical trial, Phase 3 or Phase 4 clinical trial, true?

A Correct.

Q These are not postmarketing surveillance reports --

A No.

Q -- or after the marketing of the vaccine?

A Correct.

Q We're in agreement on that?

A Yes. That's how you can have people on placebo.

Q Right.

A You would not have spontaneous report of a

placebo in the community.

Q Right. And I just want to make sure we're clear. So you talk about in regard to this table, you say, "Still, as the table below shows, there have been no reports of systemic JIA in the vaccinated population."

A Yes.

Q And so, Dr. Rose, if you'll tell me where does SJIA appear in this table?

A There's no report. There's no listing. The list, well, they get reported, so they would not put an item that has zero cases.

Q And isn't it true that in clinical trials in terms of the adverse events that are reported there is a very defined criteria of what's being looked for in a clinical trial, true?

A During the trial, yes.

Q Okay.

A During the trial.

Q Well, the trials in fact were varied in duration, but they ranged from as few as 60 days to five years. Isn't that true, sir?

A Probably. I'll take your word.

Q So for the Phase 3 clinical trials where patients were followed 4.5 years or more, you wouldn't

expect to see SJIA in those patients because of the length of time between vaccination and the posttrial time period. Isn't that true?

A I don't know why you're asking that question. Why wouldn't I see them if they are secondary to the vaccine?

Q If the Gardasil vaccine was administered early in the trial during the ordinary course of zero days, two months, six months, right?

A Correct.

Q And then those patients were followed for many years.

A Yes.

Q And you say there were no reports of SJIA in these patient populations, true?

A True.

Q But isn't it true the reason for that is, at least one reason is the length of time between vaccination and when these reports would have been made?

A This was a continuous surveillance from the time of the vaccine, including the data from the intratrial and then the posttrial. So if these individuals -- any of them, one of them -- would have suffered a permanent upregulation of IL-6 and IL-1 and

TNF via the vaccine I expect that that could present any time if the vaccine causes the disease.

Q But in the context of a clinical trial, those would have been reported if they were end points in the trial design. Isn't that true?

A Yes, but not in the posttrial -- optic neuritis were not specifically looked at except in the posttrial environment --

Q I understand.

A -- where you are more open to see things.

Q I understand.

A New events.

Q Well, let's look also at the number, 10,706 Gardasil patients.

A Yes.

Q Do you see that?

A Yes.

Q And in light of our discussion about the background rate of SJIA, .5 to one per 100,000, isn't it true that you wouldn't expect to see any cases of SJIA in --

A If it's caused by the vaccine, I don't know how many I would expect. You're giving me the background population unrelated to the vaccine as my guiding point. You're using the prevalence that we

use in nationwide studies independent from the vaccine, but if the vaccine has anything to do with the disease I don't know how many, but I would expect to see some if it is causing it. How many depends on how convinced you are that the vaccine produces the disease.

So you're using the prevalence data of the nonvaccinated and you're extrapolating it to this. I don't know how many I would expect to see. It depends on how strong the consolid (phonetic) is.

THE COURT: But the math doesn't really work because suppose if we had an incidence rate of one per 100,000.

THE WITNESS: Yes.

THE COURT: So that group of 100,000, we can divide that into 10 groups of 10,000, right?

THE WITNESS: Yes.

THE COURT: So in the SJIA people there'll be nine groups of 10,000 who have zero SJIA.

THE WITNESS: Cases.

THE COURT: Right.

THE WITNESS: Correct.

THE COURT: But we're only giving the Gardasil to one group of those 10, so wouldn't --

THE WITNESS: I'm not sure that I follow.

I'm not sure if I follow your question. I don't believe that Gardasil produces systemic JIA so I expect to see zero in both vaccinated and unvaccinated if you are using a denominator of 100,000.

I know how many JIAs I have and I know my catching area is one million children and I know that I see exactly as many as I expected to see in my clinic, so I believe this data in terms of one in 100,000 actually in my own experience. The fact that I don't see any in the right column, in the placebo column, makes sense to me.

THE COURT: But if you just had 10,000 people, how many cases of SJIA would you expect to see?

THE WITNESS: Well, I can't give you the confidence intervals. I can tell you how many I see. I have a million children -- and this is children, what we're looking for. Fifteen percent of 400. That's what I see in systemics at this present time. What would that be? Something about 60 patients with systemic JIA I follow in one million children.

THE COURT: Sure, but with only having 10,000 children you would expect to see zero cases because you only get one in 100,000.

THE WITNESS: Correct.

THE COURT: So you mostly likely get zero or --

THE WITNESS: Yes. In the placebo group.

THE COURT: No. In all groups. Just randomly out of 10,000 you would likely get zero.

THE WITNESS: Zero is a good number for that kind of patients, yes.

THE COURT: Right. So the fact that you didn't get any, out of that 10,000 you didn't get after Gardasil either, doesn't really show us anything because you were expecting zero anyway.

THE WITNESS: I would, but those who think it's a cause of the disease should expect more. How many? Well, those who propose that this disease is caused by the vaccine should have an approximation how many patients they expect to see. I expect to see zero in both columns because I don't think the vaccine has anything to do with the disease and because this denominator allows for zero as a likely outcome, but I tell you there are other conditions like uveitis, for example, that you can see which is probably of the same -- I don't remember, but I'm pretty convinced.

I've got to look at it, how many uveitis patients are in the population. But if it isn't as low as systemics it's close, and they have seen

uveitis in both cases, and uveitis was certainly not an outcome measure in the trial. So this is catching diseases that are unusual. If there have been cases, they would have been caught.

I don't know if you understand what I'm saying. If you look at the list of conditions that are listed on the left, there are many that are very rare and they are still seen on both sides. Example, optic neuritis, scleroderma. Scleroderma and morphea, for example. That's a one in a million. So the prevalence of scleroderma in children is one in a million, and you have here two cases and one case on the other side.

Now, if you run the confidence intervals here you may not find a difference, but zero is as likely as one is as likely as two. When the vaccine has nothing to do with this, you expect to see the same in both columns. I don't know if I'm answering your question.

THE COURT: I think so. Sorry, Ms. O'Dell.

MS. O'DELL: Thank you.

BY MS. O'DELL:

Q Dr. Rose, let me ask you to turn to Exhibit 26. You talked about that at length, the Pinto article.

A Yes. 26. Give me one second. Are we going to that table?
Q Correct.
A Uh-huh. That table. I got it here.
Q Are you there, sir?
A Yeah. I got it.
Q Okay.
A I have it.
Q Great. You testified regarding the Media column on the left-hand side.
A Uh-huh.
Q The Media group.
A Yes.
Q And that there was no increase in cytokines and TNF-a, IL-6, IL-1B. I believe you mentioned that one.
A Uh-huh.
Q Is that right? Did I understand your testimony correctly?
A Absolutely. When you look at zero, two and seven months times.
Q But, sir, when you look at the Media column isn't it true that what you're measuring at this point in the Media column is -- well, let me ask you. When you measure cytokines you have to measure them in

terms of not an intracellular measure. It's when they have been elucidated or activated that you begin to measure the increase from one point to another. Isn't that true? If you don't understand my question, I can --
A Oh, I can answer the question. If I take a patient with systemic JIA and measure the IL-6 levels on day one before treatment they would be high. Intra, extra, everywhere. Serum, plasma, wherever you look.
Q Right. But in this particular column when you were talking about the media --
A Yes?
Q -- and the measure of cytokines, there's been no antigen that has elucidated a proinflammatory cytokine response. Isn't that true?
A I can tell you that there's no antigen exposure with media. Yes.
Q So the fact that we don't see an increase in cytokines in the Media column is not relevant --
A Oh, I don't agree with you.
Q -- to the discussion we've had today. Isn't that true?
A Oh, I absolutely disagree with that.
Q But you would agree that in the Media column

there's been no introduction of an antigen in these patients, true?
A Could you repeat your question, because I don't think I agree with you?
Q In the Media column --
A Yes?
Q -- they have been vaccinated, but they have not been vaccinated with an antigen. Isn't that true?
A They have received --
Q They have not received an antigen. Isn't that true?
A Well, it's a vaccine. The first column is vaccinees. The third column is placebo. So you have Column 1, 2, 3. Column 3, Media, Vaccine. Column 4, 5 is Media, Placebo.
Q Right.
A So these have been vaccinated.
Q But the media does not include an antigen, does it, sir?
A Well, I don't know the exact composition of the media, but it doesn't contain the L-1 antigen at least.
Q Would you repeat that?
A Yes. It doesn't contain the L-1 antigen at least. I don't know if it contains other antigens

because I don't know what the composition of the media is.
Q Right.
A Usually you don't put the putative antigen that you are testing in the media.
Q But when you say the VL, you're talking about the virus-like protein that we see that's in the remainder of the table, L-1.
A Correct.
Q That's right. And then we see --
A L-1/10 and L-1/1.
Q Correct.
A The concentrations in micrograms that they use.
Q But the antigen I'm talking about in the media is the adjuvant that was included in the others. There's no adjuvant in the Media column, is there?
A Correct. I suspect that if you put an antigen then you cannot use these as controls.
Q Sure. And so if that is the case, which we've agreed that it is, then you would not expect to see an increase in cytokines in that --
A If the vaccination had produced systemic JIA and this is going to be used as an argument in favor, these normal individuals at least have not had a

sustained increased spontaneous release of cytokines into the supernatants. This is what I take from this table as the data.

I don't know what is your question. Of course, when you stimulate with an antigen you get more of it, but that's not what I'm talking about. I'm talking about the comparison between time zero, two and seven in what we will call baseline conditions or basal conditions or base conditions without the addition of the antigen into the soup, into the ex vivo experiment. These individuals at least have not a sustained cytokine response. This is the only in vitro study we have with HPV. That's all we have. We used the evidence that we have.

THE COURT: Ms. O'Dell, one of your earlier questions suggested that you were measuring I think you said like intracellular activity in cytokines. And I don't know if that's true, but the image I have of that is that the cytokines are somewhere in the cell, and they're almost hidden. And I think your question is saying that they need to do something to make them active, and once they're active you can count them.

MS. O'DELL: Correct.

THE COURT: Okay. I don't know if that's

true or not, but I'm trying to think of what -- so like if you're camping out in the woods at night and you look at your tent, outside of your tent, there's nothing there, but then you shine your flashlight and you see all the little gnats. And once you shine your light on them, you can count the gnats. I think what Ms. O'Dell might be saying is that until you do something like shining the light on the cell, by stimulating them, you can't count. There are cytokines present, but you can't count them because you can't see them. Is that kind of what you're saying?

MS. O'DELL: They've not been activated.

THE COURT: Right.

MS. O'DELL: That's my point.

THE COURT: Okay. Now, I think that your foundation point that you need to activate the cytokines before you can count them, I understand that you're saying that. I'm not sure that Dr. Rose is agreeing with that, or we may need to hear from Dr. McCabe about that. I'm not sure.

In my experience as a Special Master I haven't heard any testimony pro or con on that point so I don't know if that's true or not, but it seems like that's the foundation of your line of questions,

that you need to activate them before you can count them, but I'm not sure that that's true.

MS. O'DELL: I understand, Your Honor, and I can talk further with Dr. Rose about this, but let me ask because I don't know the answer to this question. Do I have an opportunity to call Dr. McCabe back to the stand in a short rebuttal on this point?

THE COURT: Oh, yes. Oh, sure.

MS. O'DELL: Okay.

THE COURT: Yes.

MS. O'DELL: Well, then that's what we'll do then.

THE WITNESS: Can I wrap up, or is that unnecessary? Everybody has a full understanding of what I meant in this analysis of the column?

THE COURT: I'll tell you my understanding. That under the theory that Gardasil produces systemic JIA through the stimulation of IL-6, you would think that the IL-6 levels would have to be sustained because people who suffer from SJIA continue to suffer from SJIA, which suggests that they too would have elevated IL-6 levels.

And to you, that people who were vaccinated, their levels, their elevation levels, don't stay high -- they drop -- which means that there's an initial

boost and then it drops down, and since it drops down but the disease continues you think that that initial boost couldn't have caused the disease.

THE WITNESS: Correct. If we had seen a signal like that this would have been a very dangerous vaccine. When you get vaccinated you want a profound cytokine response to make the antibody and you want that cytokine response to go down. I wish we could do the same thing with the systemics that we treat every day, but it's not possible so far. So, yes. I think you understood.

THE COURT: I'm not saying I agree with it.

THE WITNESS: No, no. No, no, no. But I want to make sure because it's not complicated, I think.

BY MS. O'DELL:

Q Dr. Rose, we'll turn away from the Pinto paper --

A Thank you.

Q -- at this point. Let me turn your attention to page 2 of your report and to the statement you make in the first paragraph, the second sentence I believe. You say:

"Currently, based on its clinical features and gene expression profile, it," and you're referring

to SJIA, "has emerged as one of the autoinflammatory diseases to likely associated when disregulation of cytokine networks like L-1 and L-6 networks rather than the adaptive immune system with which most of us are familiar with in discussing vaccine associated with adverse events."

Sir, tell me. When you refer to clinical features in this statement, what are you referring to?

A The clinical features of systemic JIA.

Q Can you be specific? What are examples of clinical features you're referring to?

A The clinical features of systemic JIA include hectic fever. Hectic, H-E-C-T-I-C. Hectic fever, which is a characteristic fever also known as quotidian fever, which you have usually two spikes in a single day followed by hypothermia after the fever.

You have a skin rash that is characteristic, a salmon color rash. You have inflammation of the lining of the lungs and the heart called pericolitis and pleuritis. You can have polyarthritis, although not always. Many times you have the systemic features without the arthritis. That's when we talk about systemic disease instead of systemic JIA.

And you have elevation of acute phase reactants, anemia, elevated sedimentation rate,

abnormal liver functions and a bunch of other things. Do you want me to give you the whole list?

Q No, sir. That's fine. And then you go on to say clinical features and gene expression profile. What do you mean by that?

A Gene expression profiles? So a gene expression profile is an experiment in which you measure in whatever medium that you're using what types of messenger RNAs you have in the medium, and that will tell you what genes are actually activated at that given time. That's gene expression profile.

Q Would the gene expression profile also include cytokines and cytokine networks?

A Absolutely.

Q Yes. Okay. Then in your supplemental report, page 2, you refer to articles that we've talked about at length today -- the Mellins article, the Pinto article -- and you say essentially these three statements are statements of hypothesis generation. These three citations, excuse me, are statements of hypothesis generation. And in doing so, Dr. Rose, you basically are saying these citations are interesting but not helpful. Is that a fair characterization of your testimony?

A Can you help me by telling me what citations

I'm referring here?

Q Yes. Exhibit 12, Prakken.

A Uh-huh.

Q Mellins, Exhibit 14, and the Ronaghy exhibit or article, which is Exhibit 15.

A Okay.

Q And essentially you're saying interesting but not helpful?

A No, no. Mellins's article is a review article, and if you look at the title it's questions and answers, more questions than answers. That is hypothesis generation. It's not giving us any new data. It's a review article. The other two I can't recall now, but it must be the same reason. Review articles don't give you new. They just tell you what's known and then they open up to new things to study.

Q But, sir, isn't it true that the Prakken article is not a review article and it does contain new data, not just hypothesis generation?

A So can I see it?

Q Oh, sure. Yes, sir.

A Can I have it because as soon as I look at it I will --

MR. WISHARD: I'm giving him 12, 13 and 15.

THE WITNESS: So that's what I was referring to. Mellins is the one I remember. So, counselor, you're asking me about the article by Salvatore Albani and Dr. Prakken, and you're asking me if I said -- what's your question? It's a review article. It's a chapter.

BY MS. O'DELL:

Q I'm sorry?

A It looks like a book chapter.

Q No, sir. I don't know. What exhibit are you referring to?

A The exhibit I don't have here.

Q Look at the bottom, sir, and tell me the --

A Exhibit 12.

Q I have a reference. You have the chapters (sic).

A Exhibit 12.

Q Twelve? Okay. Great. Twelve. No, sir, it's not a book chapter. That's an article published in the Lancet in 2011.

A Okay. It's a review article then. I said review article or chapter. So it's a review article. You don't see hypotheses. You don't see material and methods. You don't see results. You don't see discussion. You see headings and citation of the

literature. That's a review article.
Q Okay. And so your point being in your report that basically the Prakken article, this is an example. You talk about Mellins. This is another example, Exhibit 13, and we refer to 15. I'm not sure if I'm pronouncing that correctly, but the Ronaghy article.
A Ronaghy, yes. It's the Prakken's group.
Q Right.
A It's Dr. Prakken's group.
Q I see that.
A Uh-huh.
Q But Exhibit 15 is not a review article, is it, sir?
A So let's look at that because these two, I think that we agree that they are review articles, the other two.
Q I don't know that I agree with you, but --
A Oh, so --
Q -- I may come back to 12.
A Why don't we clean up each one at a time because I can't review everything at the same time, okay? Here this is not a review article.
Q Correct. New data is included in this article. Isn't that true, sir?

A Say again?
Q New data has been included --
A New data is in this article.
Q -- in this article, true?
A Yes. That's correct.
Q And so these articles are more than just hypothesis generation. Isn't that true, sir?
A For the causality issue I report hypothesis generation. I assume that for the causality issue of HPV causing systemic JIA a hypothesis generation, not that's all I said. That's the purpose of my statement.
MS. O'DELL: Okay. Your Honor, if you could give me just a moment here?
(Pause.)
BY MS. O'DELL:
Q Dr. Rose, just a point of clarification here. You testified during your direct about Vanessia's presentation at the hospital June 24, (sic) 2008. Do you recall your testimony about that?
A Yes, I do.
Q And you testified that she had a rash upon presentation at the hospital. Do you recall that testimony today?
A Yes, I do.

Q And I don't know if you have Exhibit 4 in front of you, sir, but according to the history and physical that was taken when she presented to the hospital, Exhibit 4, page 7, the rash that she previously had in earlier June had resolved, had it not, sir?
A I'm almost ready to say yes, when she was put on corticosteroids, if I'm not wrong.
Q And I guess my point, just to clarify, is you testified that when she presented to the hospital that she had a rash at that time?
A I think I said that she had a history of a rash. I don't know that the rash was found on the physical examination.
Q So I think the records will bear this out. If the records state that her rash had resolved upon her presentation on June 28, 2008, you have no reason to disagree with that, do you?
A I just need the question again.
Q Okay. On June 28 when she presented to the hospital, according to the records, her H&P, which is I believe page 7 of Exhibit 4, the rash that Vanessia previously had had resolved, and your testimony earlier suggested that she still had rash upon presentation to the hospital.

A Yes. Presentation is not for physical exam. Presentation is the onset of the symptoms, at least in clinical medicine. If you tell me that you have fever for 20 days today, I would say that the onset of your disease was 20 days ago and you started with fever, correct, even if I don't see the fever that day because you took a Tylenol. Do you understand what I'm saying? One thing is what you find on the physical and another thing is what you find in the history.
Q I understand. Okay. Thank you, sir.
A Sure.
MS. O'DELL: Just a moment. Your Honor, I've lost a piece of paper. If you could give me just a second to find that.
THE COURT: Sure.
MS. O'DELL: That's never a good feeling.
THE COURT: Yes. If you've only lost one you're doing pretty well.
MS. O'DELL: Well, so far. So far. One that I know of.
(Pause.)
MS. O'DELL: That's all, Your Honor. Thank you. Thank you, Dr. Rose.
THE WITNESS: Sure.

THE COURT: Why don't we take a brief comfort break, and we can come back in maybe 10 minutes or so.

THE WITNESS: Sure.

(Whereupon, a short recess was taken.)

THE COURT: Ms. O'Dell, did you happen to find that elusive piece of paper?

MS. O'DELL: No, sir, I didn't, and so I'm done.

THE COURT: Okay. Dr. Rose, thank you for testifying. I'll try to ask you some of the questions that I also asked to Dr. McCabe. Can you tell us what you did as far as becoming involved in the case, how you went about the process of writing your initial report? Similarly, I assume that Mr. Wishard or someone from his office contacted you.

THE WITNESS: Usually I get contacted first by an M.D. from the Vaccine Program and they give me a little summary of the case. Usually if I have time I accept it, and I just receive the records and review them.

THE COURT: And have you testified outside of the Vaccine Program?

THE WITNESS: Oh, boy.

THE COURT: Well, let's make it easier.

Like in the last five years.

THE WITNESS: No.

THE COURT: And what percentage of your income comes from working in this medical/legal environment?

THE WITNESS: It depends on the year really significantly. There have been years I have two cases, three. Others like this year it's a lot more, so it can be up to 10, 15 percent of my income this year.

THE COURT: Do you know what a VAERS report is, Vaccine Adverse Event Reporting System?

THE WITNESS: Yes. Yes.

THE COURT: Have you ever submitted a VAERS report?

THE WITNESS: Have I ever seen it?

THE COURT: No. Submitted for one of your patients. Have you submitted a VAERS report?

THE WITNESS: No.

THE COURT: And about how many patients have you treated with systemic juvenile idiopathic arthritis?

THE WITNESS: Perhaps 150 in my -- perhaps 200. I'm not very good at doing guess calculations. I know it's 15 percent of my population, and I have

600 JIA patients that I follow.

THE COURT: Regarding talking a little bit about cytokines, are there other diseases besides SJIA that are associated with increases in interleukin-1 or interleukin-6 and TNF alpha?

THE WITNESS: Yes.

THE COURT: What would be some of the other diseases?

THE WITNESS: Sarcoidosis, systemic lupus.

THE COURT: We have had some testimony about like the Pinto article showing that Gardasil or a Gardasil-like vaccine triggers increases in IL-6 or TNF alpha. What else or what does trigger increases in interleukin-1 or TNF alpha? What other substances trigger those?

THE WITNESS: What other in addition to?

THE COURT: Gardasil or Gardasil-like vaccines.

THE WITNESS: I suspect that almost any -- from a slap in your face to a sunburn to a pneumonia, diarrheal diseases, Crohn's disease. These are the ways we tell one cell to the other what to do, so it's very ubiquitous and it's almost a universal response, quite end specific, by the way.

THE COURT: Do you think on a more likely

than not basis that IL-1 and IL-6 and TNF alpha contribute to the onset of systemic JIA?

THE WITNESS: The onset? I would say the disease itself, absolutely. In this case you are referring to?

THE COURT: No. I'm talking about what we know about the pathogenesis of systemic JIA in general. Not about Ms. Koehn's case specifically, but about just that --

THE WITNESS: The relevant cytokines in the mix of elements that are in the pathogenesis of the disease.

THE COURT: Those relevant cytokines are IL-1 and IL-6 and TNF alpha?

THE WITNESS: Yes, but by no means the only ones that are relevant, and those are particularly highlighted because we have treatments for them that have been effective.

THE COURT: Do we have ideas what triggers the IL-1 or the IL-6 or the TNF alpha in other cases of SJIA?

THE WITNESS: No. I don't know of -- triggers or the need for triggers? There is the possibility that this disease starts by reaching a critical mass of upregulation state, and there is no

such thing as a trigger.

I think that we tend to use the concept of trigger because we are consolids (phonetic) by nature, the human beings. We think about immediate courses as from Platonic times, so we want to attribute something to something, but the truth is it is a cell or a set of macrophages that are upregulated. They get to a point that they're so upregulated that you see the symptoms. It's just a question of a critical mass situation without any intervening factor, something that we know, for example, for lupus.

THE COURT: On the timing part of the case, Dr. McCabe says that he thought that the appropriate interval between vaccination and onset of symptoms for some of the vaccination cause would parallel when we see the immune response to the vaccine, so he said since we see immune responses to the vaccine that go out six months that he thought that the interval would be within six months. Would you agree with that approach, that if you were to assume that there would be causation you would see it in six months because that's when the --

THE WITNESS: Actually if we are postulating an upregulating of the cytokines via the toll-like receptors or the nontoll receptors, from stimulus to

response is a question of hours. It's not a question of weeks.

Example, the studies in vivo where you use lipopolysaccharide or MDP to tickle the cells. You see IL-6 response in minutes, and in systemic JIA variation of IL-6 levels in hours. So I do have a problem with saying two weeks, three weeks or four weeks. This is more what we know about the adaptive immune response, but you know that in order to build a level of IgG you normally need three or four weeks. That is correct. I assume it's correct. I'm not an immunologist.

And that is one of the aspects of the attribution to the upregulation of cytokines. I just don't know why after the first vaccination or immediately after the second she didn't have an upregulation of cytokines that were so visible clinically like in fever or any other adverse event. It would be more believable if she started right away and then stayed with systemic JIA than with these lapses if we are thinking about the innate immune system.

THE COURT: I think Dr. McCabe said in his testimony this morning that the purpose of the adjuvant is to increase the cytokines associated with

the adaptive immune system. Would you agree with that statement?

THE WITNESS: Yes. They collaborate with the adaptive immune system.

THE COURT: In the Pinto article, Exhibit 26, Dr. McCabe talked about he used the study from the whole blood saying that avoids a need to isolate PMBC, I think.

THE WITNESS: Uh-huh.

THE COURT: Do you agree? Any problems with using the whole blood?

THE WITNESS: No. Actually, when you start manipulating and to extract the PMBCs, because the cytokines are so finicky, so quick, you can get false results. So I think, yeah, what he said about the total blood I agree.

THE COURT: Do you know what type of cytokines the Menococcal C vaccine elicits?

THE WITNESS: No.

THE COURT: Do you know what type of cytokines that MMR vaccine elicits?

THE WITNESS: No.

THE COURT: I haven't looked at your CV, but I assume that you're a member of some like rheumatological associations or something like that?

THE WITNESS: Yes.

THE COURT: When you attend conferences or meetings of people in the rheumatological field, have you heard people propose the idea that Gardasil causes SJIA?

THE WITNESS: Not that I recall.

THE COURT: Have you heard people talk about like whether any vaccines cause SJIA?

THE WITNESS: I would say not that I recall. That's a more general topic. I could have heard.

THE COURT: You talked about there being mouse models. You mentioned one of them was at Leuven and one of them was at Penn.

THE WITNESS: University of Leuven, L-E-U-V-E-N, in Belgium, and another one at Penn, yes.

THE COURT: So these are mouse models for what type of disease?

THE WITNESS: Macrophage activation syndrome, a condition very closely related to systemic JIA, although not the same.

THE COURT: Okay. Would it be possible to give like those mice -- the mouse models, the mice -- like the Gardasil vaccine?

THE WITNESS: Yes. I suspect you could get permission from the investigators. Yes.

THE COURT: Well, I guess what I'm asking you is this question. Is there like a mouse model for an HPV vaccine?

THE WITNESS: Not that I know. These are spontaneous macrophage activation syndrome animals that have -- at the time we were discussing the ability of this vaccine to induce or to deteriorate or worsen some signals, so I thought that that would be a good way to start, the ones that are spontaneous having symptoms of the disease, if the vaccine does make them worse. It will answer that initial question.

THE COURT: And Mr. Wishard asked you if you were on a grant review committee or a funding committee and people came to you with the hypothesis that Gardasil vaccine causes SJIA, I think you said that you would want to test other hypotheses first.

THE WITNESS: Other hypotheses first. Oh, yes. Of course. In other words, if I had funding I would go for and have an interest in looking at the cause of JIA. I will try to expand on the genetic studies or gene expression studies, which we have been seeing some good results so far. At least they give us these marvelous three drugs. So I will focus on that kind of thing more than vaccine induced disease

only because I don't see evidence to embark on such a research study.

THE COURT: You testified that in your patients who have SJIA you recommend that they get the HPV vaccine.

THE WITNESS: Correct.

THE COURT: What's the basis for your recommendation?

THE WITNESS: Prevent cancer. These are patients who are on immune suppressive drugs that could make them more prone to get cancer.

THE COURT: Is there any -- I'm not sure what the right word is -- like policy statement by like American College of Rheumatologists on this point following a group directive, as opposed to your personal opinion? Or maybe there's something in between. That's what I was kind of looking for.

THE WITNESS: It's more opinion between -- you see it in -- well, I would say in between, but I do not have it at the top of my head their recommendations. In general, if you look at the red book, the red book is the infectious disease book that makes recommendations for pediatrics, vaccination and otherwise, and those vaccines that are either inactivated or recombinant are recommended for

patients with immune suppressing medication.

THE COURT: In Verstraeten, which is Exhibit E --

THE WITNESS: Eight you said?

THE COURT: E.

THE WITNESS: Oh, E. Okay.

THE COURT: Verstraeten.

THE WITNESS: Oh, yes. Yes.

THE COURT: In Table 2 --

THE WITNESS: One second. Yes.

THE COURT: -- in the group of musculoskeletal conditions --

THE WITNESS: Yes.

THE COURT: -- there's juvenile arthritis.

THE WITNESS: Yes.

THE COURT: Does juvenile arthritis encompass SJIA?

THE WITNESS: I expect it does.

THE COURT: And why would you expect that it does?

THE WITNESS: Because it's one of the forms of juvenile arthritis.

THE COURT: And then how about on Table 3? Would SJIA fall within any of those conditions?

THE WITNESS: No.

THE COURT: When Ms. Koehn was getting treated at UCLA, she got treated by Dr. McCurdy. Do you know of Dr. McCurdy or know Dr. McCurdy's reputation?

THE WITNESS: I know him by name, but not personally.

THE COURT: Do you know what his reputation is?

THE WITNESS: No.

THE COURT: And how about Dr. Hoffman, who is also a pediatric rheumatologist at UCLA?

THE WITNESS: Doctor?

THE COURT: Hoffman.

THE WITNESS: I don't remember. It may be somebody younger than my group or older.

THE COURT: If we could turn to Exhibit 5, which is from the UCLA records? And then I have a question about page 27, I think.

MR. WISHARD: Your Honor, may I approach the witness --

THE COURT: Sure.

MR. WISHARD: -- to give him a copy? Page 27 you said, sir?

THE COURT: Yes. I'm sorry. Actually 28.

MR. WISHARD: Exhibit 5, page 28.

THE COURT: Yes.
THE WITNESS: Thank you. Oh, my God. It is a little hard for me to read this, but if you want to read me part I can --
THE COURT: I want to read you the gloss of the left-hand margin.
THE WITNESS: Left-hand? Okay. Oh, that handwritten?
THE COURT: Right.
THE WITNESS: Oh, my God.
THE COURT: I think it says: Patient mother refused flu vaccine this year. Discussed with mom importance of this vaccine. Mom hesitant because Gardasil. Then it might be: D/W -- discussed with -- mom. No data, but all vaccines and infections can trigger autoimmune response. I think that's what it says.
THE WITNESS: Congratulations.
THE COURT: Do you agree with Dr. Hoffman's statement that all vaccines can trigger autoimmune response?
THE WITNESS: If the word "can" includes the most unlikely to the most likely, yes.
THE COURT: In your second report, Exhibit F --

THE WITNESS: In the supplement that I wrote?
THE COURT: Yes.
THE WITNESS: Okay. I need to get this out of here.
MR. WISHARD: Sir, if you're finished with that, the medical records, I'll take it, please.
THE WITNESS: Okay. Page 2?
THE COURT: No. Page 1.
THE WITNESS: Page 1.
THE COURT: In paragraph No. 1 the last sentence says, "The fact that similar cytokines are found in serum or systemic JIA patients and in vaccine response is more a reflection of somewhat limited at stereotypical inflammatory responses repertoire."
THE WITNESS: In mammals, yes.
THE COURT: Could you expand on that point, what you meant by that point?
THE WITNESS: Yes. So you alluded to that same when we were talking about triggers. There are about 38, 39 important cytokines. There are not an undetermined number of cytokines, but they keep being discovered more and more.
But still there is a tool that we use to protect ourself from many things or to respond to many

things from bringing blood cells to an abscess to responding to a hemorrhage produced by trauma or burns, which is very well known, very well studied actually.
And so what I mean by that is that similarities in cytokine patterns in serum or in ex vivo studies do not mean much in terms of causality. That's what I was trying to say because we can have similar patterns or cytokine levels or values in many medical conditions.
THE COURT: I think those are all of my questions, but if you could just hang on for a few minutes to see if Mr. Wishard has any followup?
MR. WISHARD: Sir, I have no followup. Thank you.
THE COURT: Ms. O'Dell?
MS. O'DELL: No, no further followup, Your Honor.
THE COURT: Okay. Thank you, Dr. Rose. You can step down.
(Witness excused.)
(Pause.)
THE COURT: Ms. O'Dell, I have a few questions that I think I might like to hear from Dr. McCabe about, but if you wanted to ask Dr. McCabe

questions first you can do that.
MS. O'DELL: I do have a couple of questions for him, Your Honor, so if that would be appropriate to call him back to the stand and I can walk him through those questions and then we can go from there.
THE COURT: Okay.
Whereupon,
MICHAEL J. McCABE, JR.
having been previously duly sworn, was recalled as a rebuttal witness herein and was examined and testified further in rebuttal as follows:
DIRECT EXAMINATION
BY MS. O'DELL:
Q Dr. McCabe, we had a discussion a few moments ago regarding the Pinto article and specifically Table 1 and in particular what is being shown by the Media column. So with that introduction, explain to us, please, what was given to the media group and what we're seeing in this table in terms of a cytokine response.
A Sure. So as I explained this morning, the Media columns refer to absence of antigen or zero L-1. As part of the experimental design, the L-1 at one microgram and at 10 microgram are added to the media, so you can think of the L-1 at one and the L-1 at 10

micrograms, the other columns, as plus media. So really the media is the common denominator there, really reflecting on that media at zero is no antigen.

The cytokines are intracellular, so this is an ex vivo analysis. It's not analogous to -- it's related, but not analogous to measuring cytokines in plasma, as Dr. Rose alluded to in patients with systemic JIA, that he'd expect that if you took a plasma sample and we looked for IL-6 that he'd find it to be elevated because in those circumstances he'd be looking at plasma.

And here there's both an in vivo part of the experiment in the analysis, as well as an ex vivo or in vitro part. The in vivo part is the comparison between immunized versus nonimmunized and then an analysis of the cytokines that are capable of being produced by the T cells or by the cells that are present in blood, capable of producing the cytokines.

The cytokines are within the cell, and a stimulus needs to be provided in the assay to cause the cytokines to be released so that then they can be measured in the media. It is possible -- not very frequent. It is possible that this kind of an assay could be done and would find the spontaneous release of cytokines, but in most circumstances when I've seen

these type of assays and have performed these types of assays myself the cytokines need to be stimulated and to release.

So it's part a product of the assay. This is an assay where that incubation period for the in vitro part of the experiment is occurring over a period of three hours, and Dr. Rose alluded to this in his answers to questions about timing relevance, the relevance of the timing of exposure to Gardasil versus -- and the induction of proinflammatory cytokines implicated in SJIA.

He had mentioned the analogous situation would be if he looked at lipopolysaccharide in an in vitro system or a mitogen like here. This is what PHA is. That's the positive control in the right-hand columns that you would expect to see it in hours and that's not the case. The case is illustrated here even with PHA that it's taking a matter of days in this type of an assay to release the cytokines. So that's my explanation.

Q And put in context the importance of that explanation as you interpret this table.

A Well, the context is that there is a sustained cytokine response, and the sustained cytokine response is coming from circumstances where

the antigen is present in vitro and being measured from samples from vaccinated individuals at two months and seven months postimmunization.

The other thing to say about that is that there also is the issue of amplification of responses, and to a certain extent we see that here a lot of times. We certainly see it between the zero and the two-month time period. But another interpretation of these data is that it's a transient response. I mean, I think that's ultimately what Dr. Rose is saying is that it's a transient response, but you don't see the spontaneous release in the presence of media.

And that's a fair consideration, but also take into consideration what I'm telling you about the assay and that you need to have the cytokines released upon stimulation to reveal their presence and -- I lost my train of thought there. And as part of the initiating event in the context of applying this now to circumstances of systemic SJIA, you would have this amplification -- you could have this amplification -- process. I think more what I wanted to get at there was the timing and the association in SJIA with cytokine release and fever being on the order of hours.

Q In terms of your opinion about the temporal

association between Gardasil and the onset of symptoms for systemic JIA, does that discussion of hours affect your opinion at all?

A No.

Q Okay. Tell us why.

A Because my opinion is based on what's measurable and what's been documented and demonstrated in the scientific literature via-…-vis Pinto here where during the timeframe where the sustained cytokine production is being measured is in a zero to two/two to seven-month time period.

Q In terms of Table 1 of the Pinto article, is there anything that you haven't expressed about this table and what it reflects about the increase in cytokines that you think you've not shared with us thus far?

A I think I've covered it all.

Q Okay. In terms of your opinion regarding temporal association, we discussed earlier the Frazer article, Exhibit 25, and then others we referenced during your previous testimony. Without going through that again, Dr. McCabe, would you summarize for us your opinion about the temporal association between Gardasil and the onset of JIA in Vanessia's case and whether that was appropriate?

A Sure, I'll summarize it. As I've said in my report and I'm sure I said on my direct testimony -- it was part of my exhibits -- the summary of that temporal association is -- hopefully I can say this as cogent as I said it earlier because it's starting to get late in the day.

The summary of that opinion is that given the expected timeframe, both expected timeframe and documented timeframe where these immunological events -- antibody responses, changes in T cell proliferation, cytokine changes -- are both, as I said, expected and being measured as documented in some of these papers, including Frazer's and others, as you've said, that that's predictable and supportive of the timeframe that the disease is developing.

MS. O'DELL: Nothing further, Your Honor.

THE COURT: Mr. Wishard?

MR. WISHARD: Sir, I have nothing further, but I would reserve the right if Dr. Rose wants to do some brief surrebuttal.

THE COURT: Dr. McCabe, do you have an opinion regarding whether macrophage activation syndrome is similar to SJIA?

THE WITNESS: I do, and my understanding I think is in line with what Dr. Rose was saying is that

it represents a subtype of SJIA. My understanding of macrophage activation syndrome is that there are examples and information that infections, viral infections, can drive and do drive that particular disease.

THE COURT: Do you know what the incidence of scleroderma is in children?

THE WITNESS: I don't.

THE COURT: Do you know what the incidence of uveitis is in children?

THE WITNESS: I don't.

THE COURT: In your theory, which I think of that being like a Part A and a Part B. Part A is Gardasil increases IL-6 and other cytokines. Part B, IL-6 causes SJIA.

THE WITNESS: And other cytokines.

THE COURT: Right. But what do the cytokines do, for example, with a disease that involves the adaptive immune system? I've heard testimony from doctors saying that the hepatitis B vaccine has homology with myelin basic protein, so when the hepatitis B vaccine is given you develop T cells that are then misdirected against a myelin basic protein, and the result is a demyelinating disease like GBS or transverse myelitis. That's the theory.

But the vaccine stimulates the production of the immune system, which then actually is the attacking part of the disease. In your theory we have IL-6 and other cytokines. What are they doing that leads to SJIA?

THE WITNESS: So, Special Master, do you remember this morning I had a figure from the Mellins article that had the cytokines centrally located and then on the bottom part a description of some of the clinical end points and things that occur in response to those cytokines, so certainly part of the answer lies in that is that these cytokines are acting -- are pleiotropic, that they act on multiple tissues.

They, for example, act on the hypothalamus to affect temperature regulation, the liver to cause acute phase reactive proteins to be released, many of those tissues. So at the level, that's the answer. To my understanding, we don't have the level of understanding as well at the cellular level in terms of immunoregulation what are these cytokines doing.

I would expect that there's interactions and cytokine-mediated interactions between cells of the adaptive immune system and the innate immune system that are somehow playing a role in the disease, but I don't think we have that information to the level of

sophistication as you just cited, for example, with myelin basic protein through molecular mimicry type responses driving T cells that produce a myelinating disease and antimyelinating disease.

THE COURT: Articles like Frazer, they're measuring antibody response.

THE WITNESS: Correct.

THE COURT: And I understand that antibody response doesn't happen right away. It takes a few days or a couple of weeks to develop the antibodies. In your theory with the Gardasil developing/ causing the cytokines and the cytokines get produced within hours, why is there a lag between the production of cytokines April 19 or something like that -- when did she have Gardasil No. 2? She had Gardasil No. 2 on April 18, so on April 19, the next day, she had elevated cytokines. Why is there a lag of some two months before she starts to have the rash?

THE WITNESS: There could be lots of reasons for that. I mean, part of it is this amplification process that I talked about before in that you've got an initiating event and that in part serves as the event that stimulates the lack of control.

So remember here that this isn't a matter of Gardasil being the cause. It's a matter of it being a

cause or a substantial contributing factor. If we go back to your analogy that you instructed earlier about the light and the electrical circuit and the different power stations, it may very well be that there's a coal-powered plant providing electricity to cause that light to shine and now the nuclear power plant is built next door and that weighs in on the total electricity that's provided, if that analogy helps.

So there's a lag. There could be a lag for that reason that there's an amplification process that's taking place. There could be a lag because in addition to providing inflammatory mediators there's anti-inflammatory mediators that are being induced by the vaccine. There's T regulatory cells that are being induced by the vaccine and all of this is -- you know, none of this was measured in Vanessia so it's difficult to get there in the context of the question you asked me.

THE COURT: In regard to Pinto, the Media column --

THE WITNESS: Yes?

THE COURT: -- so what I'm understanding you to say is that for the assay to work, to detect the cytokines, the cytokines need to be stimulated, and without L-1 in 10 micrograms or L-1 in one microgram

that you're not going to have that stimulation to excite or stimulation to release the cytokines.

THE WITNESS: Yeah. You would not. You may not. There would have to be --

THE COURT: So what's the purpose of having the Media column?

THE WITNESS: You've got to have a comparison. You've got to be able to show that you've got a valid assay. I mean, this is the experimental design. You've got to have something to compare to.

THE COURT: But you say the assay doesn't work in the media because it's not being tested. It's not being stimulated.

THE WITNESS: Yes.

THE COURT: So then how would that become --

THE WITNESS: Sure.

THE COURT: How would you come to a valid assay?

THE WITNESS: The assay is valid because the comparison within the assay is back to zero antigen. So, for example, if you just state the very first cytokine, interleukin-2, and you go over to the L-1, 10 Microgram column where the mean is seven, how would you know that seven -- or maybe I better go down one to 121. How would you know that 121 represented an

increase if there was no control to do that?

So in other words, it's not zero with media. It's some background release that's stimulated in the absence. There's no difference. Or not background release. There's some background signal that's measured. That's a more appropriate way of stating that. So you've got to have a control, an interassay control, a negative control to compare to.

THE COURT: With Ms. O'Dell you talked about this being like an in vivo experiment and then you talked about plasma. It seemed like that was something that was important to you, but I didn't understand the significance of like why the fact that something is being measured out of plasma --

THE WITNESS: Sure.

THE COURT: I think that there was a depth of knowledge that I don't have that was kind of assumed in your answer, so maybe you could kind of clarify that for me.

THE WITNESS: Dr. Rose had made a comment that in SJIA patients often times if plasma is taken and cytokines are measured that there's an increase in interleukin-6. That's a different analysis of cytokines than what's occurring here, so in that case the cytokines themselves are being measured in vivo.

They're not measuring the cytokines in plasma in the individuals who have been immunized in this experiment. They're measuring the ability of the cells in whole blood to be able to produce those cytokines so there's a little bit of disconnect in the comparison back to the application of those data to measuring cytokines, namely IL-6, in plasma in SJIA patients.

Another way of looking at it would be to do this assay, and I don't recall ever seeing anything in the literature where this is done, to take the whole blood from patients with SJIA and look for the cytokine production in this type of an assay. And I would suspect that in order to see that cytokine production in this type of assay even with interleukin-6 that the cells would have to be stimulated in some way to reveal that in the in vitro assay.

THE COURT: How do you respond to Dr. Rose's point about the chronicity I guess of SJIA in the sense that rheumatologists are continuing prescribing the anti-inflammatory medications so they would suggest to the rheumatologists that there's a continual increase of the inflammation that they need to keep under control?

We know with Gardasil that the antibodies do come down within the -- I think the immune response generated by Gardasil stops at some point, so how does like the chronicity of the continuation of SJIA, how do you answer that part of the case?

THE WITNESS: I'll answer it by I agree with him. That's my understanding. He certainly seemed to describe that well, that the cytokine disregulation in SJIA isn't a transient event, that it's ongoing. You know, appreciate that there are cytokines and cytokine control both in the beginning part of an immune response and development of a disease or response to a vaccine, and then there are efferent phases of cytokines that are being released, and sometimes there's overlapping cytokines. Oftentimes there are different cytokines.

Part of my answer also lies in what I talked about with amplification processes that are being stimulated by cytokines and being part of that amplification process.

THE COURT: I think those are my followup. Ms. O'Dell?

MS. O'DELL: Nothing further, Your Honor.

THE COURT: Mr. Wishard?

MR. WISHARD: Nothing further, sir.

(Witness excused.)

MR. WISHARD: One moment, Your Honor.

(Pause.)

MR. WISHARD: Can I just recall Dr. Rose for just a brief explanation on Exhibit 26?

THE COURT: Yes.

MR. WISHARD: Do you want to take your notes up, too?

DR. ROSE: Thank you.

Whereupon,

CARLOS D. ROSE

having been previously duly sworn, was recalled as a rebuttal witness herein and was examined and testified further in rebuttal as follows:

DIRECT EXAMINATION

THE WITNESS: I just want to take you to Table 1, the one that we are discussing on the Pinto paper, and I just circled the cytokine values. I picked TNF, IL-6 and IL-1 beta. And I go back to the media level, and then I will take you through both vertically and horizontal. Let's just start by TNF, which I think is important in this case because she was an anti TNF responder, so whatever that value of that. So if you look at the mean value of TNF in the media it's 3.8. Do you see that?

THE COURT: Yes.

THE WITNESS: When you go to the L-1, one microgram, it goes to 6.4. So it's not that we are talking three and 300. It's in some order of magnitude that is comparable. Of course, this is unstimulated so there is some release of cytokine in the baseline situation in this individual. If release is necessary to be measurable there is then release. And it's not that we're talking .038 or .0038. We're talking 3.8 and 6.4, comparable numbers.

But if you go from this TNF vertically now and you go down and you look at 3.8, 3.2 and 3.3 in this basis, so then I do see that that number is stable, even if it is unstimulated. These individuals have not been primed to make more cytokines. That is I think what I was trying all the time to explain. I don't know if I was able to make myself clear. Even if this is necessary for the design of the study, these cytokines are shown in the media.

And you can do something similar with IL-6. The value of IL-6 in the media is 36.4 and in the L-1 is 134, so it's essentially like a fourfold increase. Again, not an amount of cytokine that you can ignore. It's there. But then you look vertically and in IL-6 towards the end there is 128, but it's shown as

nonsignificant. That's the point I wanted to make on the table, that we should not ignore this left column.

And then in terms of the two-week period of latency between the vaccine and the onset of the disease I think is too much uncertainty about the potential pro and anti-inflammatory mechanisms that have been operating to say that two weeks or four weeks or six weeks is adequate.

THE COURT: So it's actually two months, not two weeks.

THE WITNESS: Two months, yes. So two months is as good as two hours or as good as six months since we really don't know what's going on.

THE COURT: Any further followup?

MR. WISHARD: No further questions.

THE COURT: Okay. Very good.

(Witness excused.)

THE COURT: Did Dr. McCabe need the last word?

MS. O'DELL: No, Your Honor. I think we're good.

THE COURT: Very good. Thank you, everyone, for your testimony. This is an important case. I appreciate all of the hard work and preparation you put in to preparing and being here today. All of your

work both makes my job easier and harder, so thank you for that.

I try to keep a list of things that were talked about during the hearing, and we have a very short list. That's good. Mr. Wishard, the only thing I think that was talked about was the excerpt from the Robson website.

MR. WISHARD: Yes, sir.

THE COURT: But I'm not even sure that that's all that significant in the overall scheme of the case.

MR. WISHARD: I can file it if the Court wants, but I don't necessarily need to do that.

THE COURT: I don't really see much of a need for that.

MR. WISHARD: Okay.

THE COURT: So what would the parties like to do next? I guess the choices are either file briefs or not file briefs.

MS. O'DELL: Your Honor, I think it would be appropriate in light of the complexity of the testimony that we've heard today to file briefs in this case.

THE COURT: Okay.

MR. WISHARD: That's fine, sir.

THE COURT: Mr. Wishard, do you have a preference on simultaneous briefing or sequential briefing?

MR. WISHARD: I have no preference one way or the other as long as we have adequate time after the transcript is issued, which is usually around 30 days, to respond.

THE COURT: Ms. O'Dell, we often put on after the transcript, which will be 30 days, and then we often put on paper a 30/30/15 briefing schedule. We often put that on paper. I'm not sure I've often seen that followed, but does that sound like a reasonable estimate to start with?

MS. O'DELL: Yes, sir. If we could start at that point that would be great. It depends on when the transcript's been made available. I have a trial of a large case on the west coast at it sounds like about the time the transcript might be available, and if that were the case I'd like to ask leave of the Court to have an extension.

THE COURT: Oh, sure. We're generous about those.

MS. O'DELL: Yes.

THE COURT: But we've got to put something down on paper to start with.

MS. O'DELL: Thank you. With that understanding, that would be fine.

THE COURT: Sure. Anything else then, Ms. O'Dell?

MS. O'DELL: No, Your Honor.

THE COURT: Mr. Wishard?

MR. WISHARD: No, sir.

THE COURT: Okay. Very good. Let's go off the record then. Thank you very much again, everyone.

(Whereupon, at 6:20 p.m., the hearing in the above-entitled matter was concluded.)

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REPORTER'S CERTIFICATE

DOCKET NO.: 11-355V
CASE TITLE: Koehn v. Secretary, HHS
HEARING DATE: June 21, 2012
LOCATION: Washington, D.C.

I hereby certify that the proceedings and evidence are contained fully and accurately on the tapes and notes reported by me at the hearing in the above case before the United States Court of Federal Claims.

Date: June 21, 2012

Gabriel Gheorghiu
Official Reporter
Heritage Reporting Corporation
Suite 600
1220 L Street, N.W.
Washington, D.C. 20005-4018

CLOSED,ECF,VAPPEAL

US Court of Federal Claims
United States Court of Federal Claims (COFC)
CIVIL DOCKET FOR CASE #: 1:11-vv-00355-EGB

KOEHN et al v. SECRETARY OF HEALTH AND HUMAN SERVICES
Assigned to: Senior Judge Eric G. Bruggink
Referred to: Special Master Christian J. Moran
Cause: 42:300 Vaccine Injury Act

Date Filed: 06/06/2011
Date Terminated: 12/09/2013
Jury Demand: None
Nature of Suit: 498 Injury - Human Papillomavirus
Jurisdiction: U.S. Government Defendant

Petitioner

CHERYL KOEHN
as Mother and Next Friend of

represented by **Patricia Leigh O Dell**
Beasley, Allen, et al.
Post Office Box 4160
Montgomery, AL 36103-4160
(334) 269-2343
Fax: (334) 954-7555
Email: leigh.odell@beasleyallen.com
ATTORNEY TO BE NOTICED

Petitioner

VANESSIA KOEHN

represented by **Patricia Leigh O Dell**
(See above for address)
ATTORNEY TO BE NOTICED

V.

Respondent

SECRETARY OF HEALTH AND HUMAN SERVICES

represented by **Darryl R. Wishard**
U. S. Department of Justice - Vaccine
Vaccine/Torts Branch, Civil Division
P.O. Box 146
Benjamin Franklin Station
Washington, DC 20044-1046
(202) 616-4357
Fax: (202) 616-4310
Email: darryl.wishard@usdoj.gov
LEAD ATTORNEY
ATTORNEY TO BE NOTICED

Date Entered	#	Docket Text

03/26/2014	66	JUDGE VACCINE REPORTED OPINION re: 61 ORDER denying Motion for Review.Signed by Senior Judge Eric G. Bruggink. (jt1) Copy to parties. (Entered: 03/26/2014)
03/19/2014	65	**SEALED**TRANSCRIPT of Proceedings held on October 18, 2013 before Senior Judge Eric G. Bruggink. Total No. of Pages: 1-69. To purchase a copy, contact the clerk's office at (202) 357-6414. (dw1) (Entered: 03/19/2014)
03/19/2014	64	Notice Of Filing Of Certified Transcript for proceedings held on October 18, 2013 in Washington, DC. (dw1) (Entered: 03/19/2014)
02/19/2014	63	CAFC Notice of Review, with CAFC case no. 2014-5054. (hw1) (Entered: 02/19/2014)
12/09/2013	62	JUDGMENT entered, pursuant to Appendix B, Vaccine Rule 30, that the petition is dismissed. No costs.(Copy to parties) (dls) (Entered: 12/09/2013)
12/03/2013	61	ORDER denying 48 Motion for Review Signed by Senior Judge Eric G. Bruggink. (md) Copy to parties. (Entered: 12/03/2013)
10/08/2013	60	ORDER denying 59 Motion to Stay Signed by Senior Judge Eric G. Bruggink. (md) Copy to parties. (Entered: 10/08/2013)
10/07/2013	59	MOTION to Stay *Oral Argument*, filed by SECRETARY OF HEALTH AND HUMAN SERVICES.Response due by 10/24/2013. (Matanoski, Vincent) (Entered: 10/07/2013)
08/30/2013	58	REVISED SCHEDULING ORDER: **Oral Argument is rescheduled for 10/18/2013 at 10:00 AM in the National Courts Building before Senior Judge Eric G. Bruggink.** Signed by Senior Judge Eric G. Bruggink. (md) Copy to parties. (Entered: 08/30/2013)
08/23/2013	57	SUR-REPLY re 48 MOTION for Review of 47 DECISION of Special Master *Christian Moran* , filed by SECRETARY OF HEALTH AND HUMAN SERVICES. (Wishard, Darryl) (Entered: 08/23/2013)
08/15/2013	56	SCHEDULING ORDER: **Oral Argument on Plaintiff's Motion for Review is set for 10/15/2013 at 10:00 AM EST in the National Courts Building before Senior Judge Eric G. Bruggink.** Signed by Senior Judge Eric G. Bruggink. (md) Copy to parties. (Entered: 08/15/2013)
08/07/2013	55	ORDER denying 54 Motion to Strike; granting 52 Motion for Leave to File Reply Signed by Senior Judge Eric G. Bruggink. (md) Copy to parties. (Entered: 08/07/2013)
08/07/2013	54	MOTION to Strike 53 Reply to Response to Motion *and Response to Petitioner's Ex Parte Motion for Leave to File a Reply in Support of Motion for Review*, filed by SECRETARY OF HEALTH AND HUMAN SERVICES.Response due by 8/26/2013. (Wishard, Darryl) (Entered: 08/07/2013)
08/05/2013	53	REPLY to Response to Motion re 48 MOTION for Review of 47 DECISION of Special Master *Christian Moran* , filed by CHERYL KOEHN, VANESSIA KOEHN. (O Dell, Patricia) (Entered: 08/05/2013)

08/05/2013	52	Ex Parte MOTION for Leave to File Reply , filed by CHERYL KOEHN, VANESSIA KOEHN.Response due by 8/22/2013. (O Dell, Patricia) (Entered: 08/05/2013)
08/05/2013		ORDER granting 49 Motion for Leave to File Excess Pages. Reciprocal leave is granted to respondent as well. Signed by Senior Judge Eric G. Bruggink. (jpk1) Copy to parties. (Entered: 08/05/2013)
07/29/2013	51	RESPONSE to 48 MOTION for Review of 47 DECISION of Special Master *Christian Moran* , filed by SECRETARY OF HEALTH AND HUMAN SERVICES. (Wishard, Darryl) (Entered: 07/29/2013)
07/02/2013		Case assigned to Senior Judge Eric G. Bruggink. (dls) (Entered: 07/02/2013)
07/02/2013	50	NOTICE of Assignment to Senior Judge Eric G. Bruggink. (dls) (Entered: 07/02/2013)
07/02/2013	49	MOTION for Leave to Exceed Page Limit of Motion for Review by 7 pages , filed by CHERYL KOEHN, VANESSIA KOEHN.Response due by 7/19/2013. (O Dell, Patricia) (Entered: 07/02/2013)
07/01/2013	48	MOTION for Review of 47 DECISION of Special Master *Christian Moran*, filed by CHERYL KOEHN, VANESSIA KOEHN.Response due by 8/1/2013. (O Dell, Patricia) (Entered: 07/01/2013)
05/30/2013	47	DECISION. Signed by Special Master Christian J. Moran. (tm) Copy to parties. (Entered: 05/30/2013)
12/04/2012	46	POST HEARING BRIEF by CHERYL KOEHN, VANESSIA KOEHN. (O Dell, Patricia) (Entered: 12/04/2012)
11/19/2012	45	POST HEARING BRIEF by SECRETARY OF HEALTH AND HUMAN SERVICES. (Attachments: # 1 Exhibit H, # 2 Exhibit I, # 3 Exhibit J)(Wishard, Darryl) (Entered: 11/19/2012)
10/03/2012	44	ORDER granting respondent's motion for an enlargement of time to file her post-hearing brief. Respondent shall file her post-hearing brief by 11/26/2012. Petitioner may file a reply post-hearing brief 15 days later. Signed by Special Master Christian J. Moran. (jc3) Copy to parties. (Entered: 10/03/2012)
10/03/2012	43	STATUS REPORT *and Motion for Enlargement of Time*, filed by SECRETARY OF HEALTH AND HUMAN SERVICES. (Wishard, Darryl) (Entered: 10/03/2012)
09/21/2012	42	POST HEARING BRIEF by CHERYL KOEHN, VANESSIA KOEHN. (O Dell, Patricia) (Entered: 09/21/2012)
09/07/2012	41	SCHEDULING ORDER: The Secretary is ordered to file Appendix A to the Chao article. The Secretary should also present a short statement from Dr. Rose, explaining what the algorithm shows in relation to sJIA. The deadline for the Secretary's submission of both the article and Dr. Rose's supplemental statement is the same date as the Secretary's post-hearing brief. Signed by Special Master Christian J. Moran. (jc3) Copy to parties. (Entered: 09/07/2012)
07/31/2012	40	

		ORDER granting 39 petitioner's motion for an extension of time to file a post-hearing brief. Petitioner shall file her post-hearing brief by 9/21/2012. Respondent shall file a post-hearing brief 30 days after receipt of petitioner's brief. Petitioner may file a reply brief 15 days later. Signed by Special Master Christian J. Moran. (jc3) Copy to parties. (Entered: 07/31/2012)
07/26/2012	39	MOTION for Extension of Time until 9/22/12 to File Post-Hearing Brief, filed by CHERYL KOEHN, VANESSIA KOEHN.Response due by 8/13/2012. (O Dell, Patricia) (Entered: 07/26/2012)
07/24/2012	38	TRANSCRIPT of Proceedings held on June 21, 2012 before Special Master Christian J. Moran. Total No. of Pages: 1-312. Procedures Re: Electronic Transcripts and Redactions. For copy, contact Heritage Court Reporting, (202) 628-4888. Forms to Request Transcripts. Release of Transcript Restriction set for 10/22/2012. (dw1) (Entered: 07/24/2012)
07/24/2012	37	Notice Of Filing Of Certified Transcript for proceedings held on June 21, 2012 in Washington, DC. (dw1) (Entered: 07/24/2012)
07/09/2012		Minute Entry for proceeding held before Special Master Christian J. Moran. A status conference was held on 7/9/2012. [Total number of days of proceeding: 1]. Proceeding was not officially recorded (For parties in the case only, click HERE for link to Court of Federal Claims web site forms page for information on ordering: certified transcript from reporter or certified transcript of proceeding from official digital recording.)(jc3) (Entered: 07/09/2012)
06/22/2012	36	SCHEDULING ORDER: Petitioner shall file a post-hearing brief 30 days after receipt of the transcript. Respondent shall file a post-hearing brief 30 days after receipt of petitioner's brief. Petitioner may file a reply post-hearing brief 15 days later. **A status conference is set for 6/28/2012 at 11:00 AM in Chambers (Telephonic) before Special Master Christian J. Moran.** Signed by Special Master Christian J. Moran. (jc3) Copy to parties. (Entered: 06/22/2012)
06/21/2012		Minute Entry for proceeding held before Special Master Christian J. Moran. A hearing was held on 6/21/2012. [Total number of days of proceeding: 1]. Official record of proceeding taken by court reporter (For parties in the case only, click HERE for link to Court of Federal Claims web site forms page for information on ordering: certified transcript from reporter or certified transcript of proceeding from official digital recording.)(jc3) (Entered: 06/21/2012)
06/21/2012	35	TRANSCRIPT of Proceedings held on June 13, 2012 before Special Master Christian J. Moran. Total No. of Pages: 1-26. Procedures Re: Electronic Transcripts and Redactions. For copy, contact Heritage Court Reporting, (202) 628-4888. Forms to Request Transcripts. Release of Transcript Restriction set for 9/20/2012. (dw1) (Entered: 06/21/2012)
06/21/2012	34	Notice Of Filing Of Certified Transcript for proceedings held on June 13, 2012 in Washington, DC. (dw1) (Entered: 06/21/2012)
06/18/2012	33	NOTICE OF FILING Documents by CHERYL KOEHN, VANESSIA KOEHN. (Attachments: # 1 Ex. 43, # 2 Ex. 44, # 3 Ex. 45, # 4 Ex. 46, # 5 Ex. 47, # 6 Ex. 48)(O Dell, Patricia) (Entered: 06/18/2012)

06/15/2012	32	NOTICE OF FILING Exhibit G by SECRETARY OF HEALTH AND HUMAN SERVICES. (Attachments: # 1 Exhibit G)(Wishard, Darryl) (Entered: 06/15/2012)
06/14/2012	31	SCHEDULING ORDER: A hearing remains set for 6/21/2012. This hearing will begin at 9:00 A.M. Eastern Time. All additional filings are due by 6/18/2012. Signed by Special Master Christian J. Moran. (jc3) Copy to parties. (Entered: 06/14/2012)
06/13/2012		Minute Entry for proceeding held in chambers [telephonic] before Special Master Christian J. Moran: Status Conference held on 6/13/2012. [Total number of days of proceeding: 1]. Official Record of proceeding taken via electronic digital recording (EDR) (For parties in the case only, click HERE for link to Court of Federal Claims web site forms page for information on ordering: certified transcript from reporter or certified transcript of proceeding from official digital recording.)(tpj) (Entered: 06/13/2012)
05/25/2012	30	PREHEARING SUBMISSIONS by SECRETARY OF HEALTH AND HUMAN SERVICES. (Wishard, Darryl) (Entered: 05/25/2012)
05/21/2012	29	Witness List, filed by CHERYL KOEHN, VANESSIA KOEHN. (O Dell, Patricia) (Entered: 05/21/2012)
05/16/2012	28	PREHEARING SUBMISSIONS by CHERYL KOEHN, VANESSIA KOEHN. (O Dell, Patricia) (Entered: 05/16/2012)
05/16/2012	27	Witness List, filed by CHERYL KOEHN, VANESSIA KOEHN. (O Dell, Patricia) (Entered: 05/16/2012)
05/16/2012	26	Exhibit List, filed by CHERYL KOEHN, VANESSIA KOEHN. (O Dell, Patricia) (Entered: 05/16/2012)
05/16/2012	25	NOTICE OF FILING documents by CHERYL KOEHN, VANESSIA KOEHN. (Attachments: # 1 Ex. 34, # 2 Ex. 35, # 3 Ex. 36, # 4 Ex. 37, # 5 Ex. 38, # 6 Ex. 39, # 7 Ex. 40, # 8 Ex. 41, # 9 Ex. 42)(O Dell, Patricia) (Entered: 05/16/2012)
03/14/2012	24	STATUS REPORT, filed by CHERYL KOEHN, VANESSIA KOEHN. (O Dell, Patricia) (Entered: 03/14/2012)
03/06/2012	23	NOTICE OF INTENT to Remain in the Program by Petitioner. (O Dell, Patricia) (Entered: 03/06/2012)
02/13/2012	22	PREHEARING ORDER: A hearing remains set for 6/21/2012 in Washington, DC. A pre-trial conference is set for 6/12/2012 at 11:00 A.M. Eastern Time. Petitioner shall file any additional medical articles and/or demonstrative exhibits by 5/16/2012, and respondent shall file any articles and/or demonstrative exhibits 14 days later. Petitioner shall file a brief by 5/16/2012, and respondent shall file her brief 14 days later. Petitioner shall file a status report regarding settlement by 3/14/2012. Petitioner should confer with respondent prior to filing this report. Signed by Special Master Christian J. Moran. (jc3) Copy to parties. (Entered: 02/13/2012)
02/08/2012	21	ORDER re: the statutory 240-day time period for the special master's issuance of a decision in this case has expired. Petitioner may submit a notice continuing

		or withdrawing the petition and such notice shall be filed within 30 days. Signed by Special Master Christian J. Moran. (tpj) Copy to parties. (Entered: 02/08/2012)
01/18/2012	20	STATUS REPORT, filed by SECRETARY OF HEALTH AND HUMAN SERVICES. (Wishard, Darryl) (Entered: 01/18/2012)
01/11/2012	19	NOTICE OF FILING Exhibit F by SECRETARY OF HEALTH AND HUMAN SERVICES. (Attachments: # 1 Exhibit F)(Wishard, Darryl) (Entered: 01/11/2012)
12/15/2011	18	SCHEDULING ORDER: Respondent shall file a status report regarding settlement discussions by 1/30/2012. A hearing is set for 6/21/2012 in Washington, DC. A prehearing confernece is set, sua sponte, for 6/12/2012 at 11:00 A.M. Eastern Time. In advance of the prehearing conference, the parties should review the record to confirm that all materials to be discussed at the hearing have been disclosed. Each party shall file a witness list and affidavits from the testifying witnesses by 6/6/2012. Respondent is reminded that Dr. Rose may file a supplemental expert report. If Dr. Rose chooses to prepare this report, this report is due by 1/13/2012. Signed by Special Master Christian J. Moran. (jc3) Copy to parties. (Entered: 12/15/2011)
12/13/2011	17	STATUS REPORT, filed by CHERYL KOEHN, VANESSIA KOEHN. (O'Dell, Patricia) (Entered: 12/13/2011)
11/29/2011	16	SCHEDULING ORDER: Petitioner shall file a status report by 12/13/2011, regarding the parties' mutual availability for a one-day hearing in Washington, DC, to take place in either May or June 2012. In this same status report, petitioner shall provide an update on the status of settlement discussions. Petitioner shall indicate whether she has communicated a demand. Dr. Rose may file a supplemental expert report. If Dr. Rose chooses to prepare this report, this report is due by 1/13/2012. Signed by Special Master Christian J. Moran. (jc3) Copy to parties. (Entered: 11/29/2011)
11/29/2011		Minute Entry for proceeding held before Special Master Christian J. Moran. A status conference was held on 11/29/2011. [Total number of days of proceeding: 1]. Proceeding was not officially recorded (For parties in the case only, click HERE for link to Court of Federal Claims web site forms page for information on ordering: certified transcript from reporter or certified transcript of proceeding from official digital recording.)(jc3) (Entered: 11/29/2011)
11/14/2011	15	Respondent's Report, filed by SECRETARY OF HEALTH AND HUMAN SERVICES. (Wishard, Darryl) (Entered: 11/14/2011)
11/14/2011	14	NOTICE OF FILING Exhibits A - E by SECRETARY OF HEALTH AND HUMAN SERVICES. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C, # 4 Exhibit D, # 5 Exhibit E)(Wishard, Darryl) (Entered: 11/14/2011)
10/03/2011	13	NOTICE OF FILING Supplemental Affidavit by CHERYL KOEHN, VANESSIA KOEHN. (Attachments: # 1 Ex. 27, # 2 Ex. 28, # 3 Ex. 29, # 4 Ex. 30, # 5 Ex. 31, # 6 Ex. 32, # 7 Ex. 33)(O'Dell, Patricia) (Entered: 10/03/2011)
09/13/2011	12	

		NOTICE OF FILING Scientific Articles by CHERYL KOEHN, VANESSIA KOEHN. (Attachments: # 1 Ex. 11, # 2 Ex. 12, # 3 Ex. 13, # 4 Ex. 14, # 5 Ex. 15, # 6 Ex. 16, # 7 Ex. 17, # 8 Ex. 18, # 9 Ex. 19, # 10 Ex. 20, # 11 Ex. 21, # 12 Ex. 22, # 13 Ex. 23, # 14 Ex. 24, # 15 Ex. 25, # 16 Ex. 26)(O'Dell, Patricia) (Entered: 09/13/2011)
09/02/2011	11	NOTICE OF FILING Curriculum Vitae by CHERYL KOEHN, VANESSIA KOEHN. (Attachments: # 1 Ex. 10)(O'Dell, Patricia) (Entered: 09/02/2011)
09/02/2011	10	SCHEDULING ORDER: Petitioner shall file Dr. McCabe's CV as soon as reasonably possible. Petitioner shall file the literature cited by Dr. McCabe as soon as reasonably possible, or by 9/16/2011. Petitioner shall file a complete supplemental report from Dr. McCabe by 10/3/2011. Respondent's Rule 4 report and responsive expert report are due 45 days after receipt of Dr. McCabe's supplemental expert report. A status conference is set for 11/29/2011 at 10:00 A.M. Eastern Time. Signed by Special Master Christian J. Moran. (jc3) Copy to parties. (Entered: 09/02/2011)
09/02/2011		Minute Entry for proceeding held before Special Master Christian J. Moran. A status conference was held on 9/2/2011. [Total number of days of proceeding: 1]. Proceeding was not officially recorded (For parties in the case only, click HERE for link to Court of Federal Claims web site forms page for information on ordering: certified transcript from reporter or certified transcript of proceeding from official digital recording.)(jc3) (Entered: 09/02/2011)
08/24/2011	9	NOTICE OF FILING Affidavit *of Dr. Michael McCabe, Jr.* by CHERYL KOEHN, VANESSIA KOEHN. (Attachments: # 1 Ex. 9)(O'Dell, Patricia) (Entered: 08/24/2011)
08/18/2011	8	NOTICE OF FILING Medical Records by CHERYL KOEHN, VANESSIA KOEHN. (Attachments: # 1 Exhibit 7, # 2 Exhibit 8)(O'Dell, Patricia) (Entered: 08/18/2011)
07/25/2011	7	SCHEDULING ORDER: Petitioner shall file the physical therapy records and ophthalmology records as soon as reasonably possible. Petitioner shall file her expert report by 8/24/2011. The deadline for respondent's Rule 4(c) is suspended. A status conference is set for 9/2/2011 at 10:30 A.M. Eastern Time. Signed by Special Master Christian J. Moran. (jc3) Copy to parties. (Entered: 07/25/2011)
07/25/2011		Minute Entry for proceeding held before Special Master Christian J. Moran. A status conference was held on 7/25/2011. [Total number of days of proceeding: 1]. Proceeding was not officially recorded (For parties in the case only, click HERE for link to Court of Federal Claims web site forms page for information on ordering: certified transcript from reporter or certified transcript of proceeding from official digital recording.)(jc3) (Entered: 07/25/2011)
06/16/2011	6	INITIAL ORDER: The initial status conference in this case shall be held on 7/19/2011 at 10:30 A.M. Eastern Time. Respondent's Rule 4(c) Report is due on 9/5/2011 unless otherwise modified by the court. Signed by Special Master Christian J. Moran. (jc3) Copy to parties. (Entered: 06/16/2011)
06/14/2011	5	

		AMENDED PETITION re: 1 Petition, filed by CHERYL KOEHN, VANESSIA KOEHN. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6)(O'Dell, Patricia) (Entered: 06/14/2011)
06/13/2011	4	NOTICE of Appearance by Darryl R. Wishard for SECRETARY OF HEALTH AND HUMAN SERVICES.. (Wishard, Darryl) (Entered: 06/13/2011)
06/09/2011	3	NOTICE of Assignment to Special Master Christian Moran. (Neal, Alonzo) (Entered: 06/09/2011)
06/09/2011	2	NOTICE of Designation of Electronic Case. (Neal, Alonzo) (Entered: 06/09/2011)
06/09/2011	1	PETITION against SECRETARY OF HEALTH AND HUMAN SERVICES (Filing fee $350, Receipt number 072369) [Vaccination date: 2/18/08], filed by CHERYL KOEHN, VANESSIA KOEHN. Respondents Report due by 9/6/2011. Motion to convert case to ECF.(Neal, Alonzo) (Neal, Alonzo). (Additional attachment(s) added on 6/9/2011: # 1) (Neal, Alonzo). (Neal, Alonzo). (Entered: 06/09/2011)

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